ANNALS OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND

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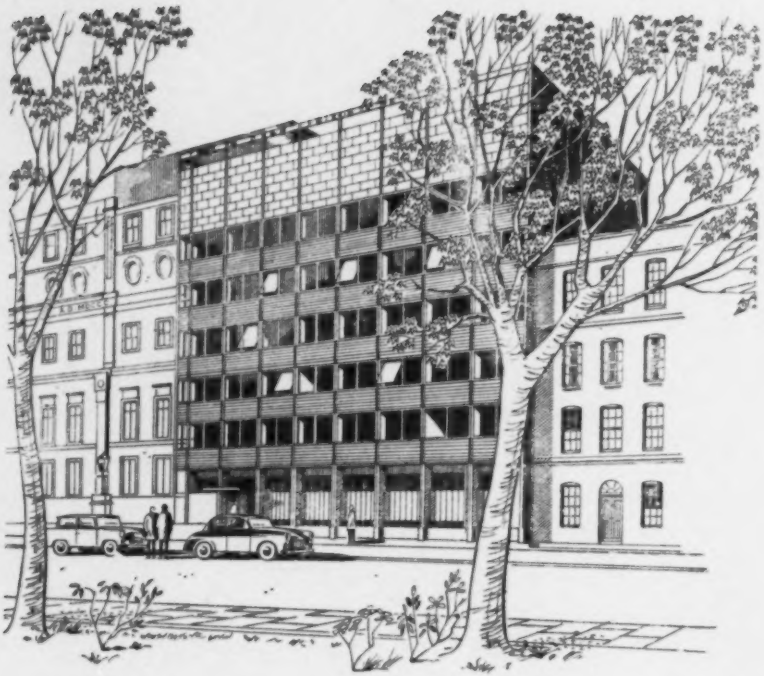

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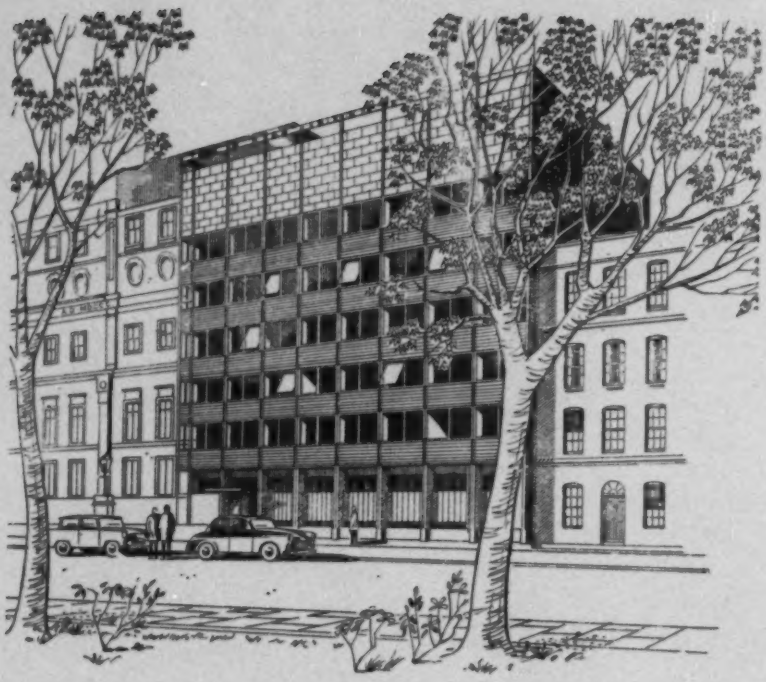

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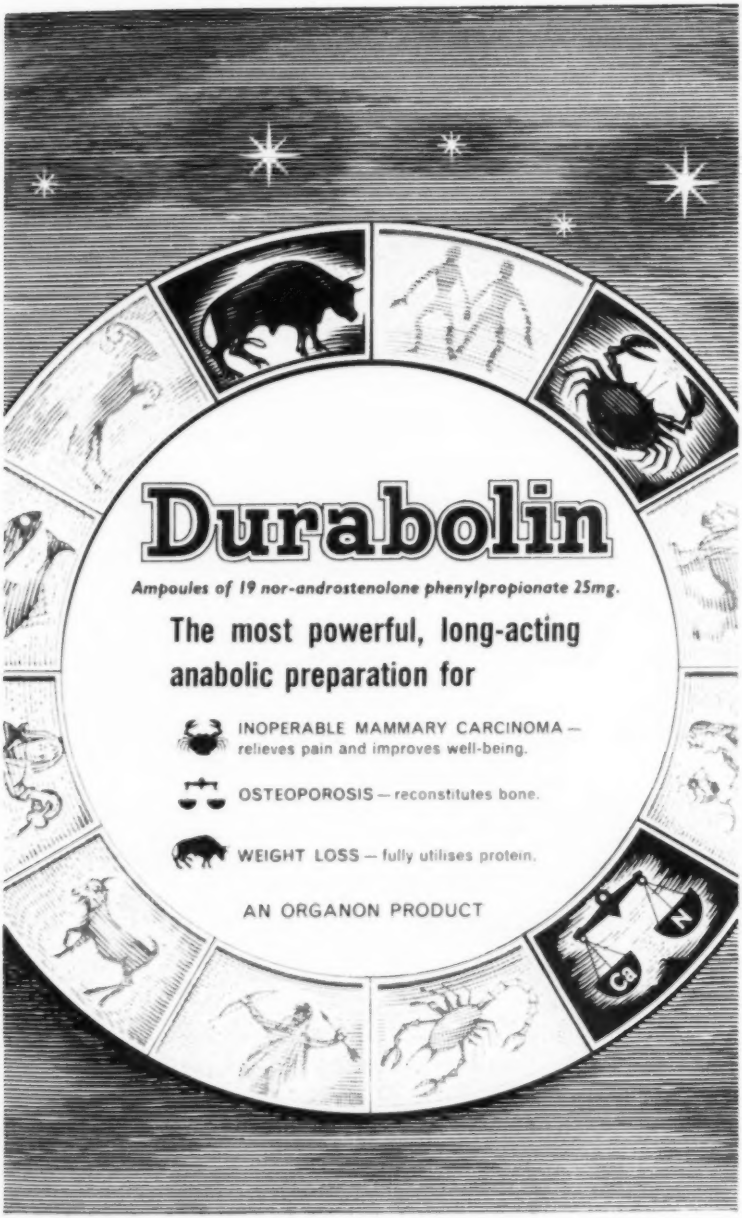
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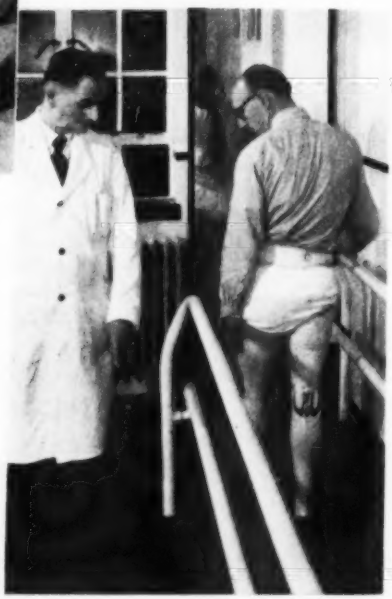

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FEBRUARY 1960

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ON THE NATURE AND CARE OF WOUNDS

Moynihan Lecture delivered at the Royal College of Surgeons of England
on
8th July 1959
by

J. Englebert Dunphy, M.D.*

Professor of Surgery, Harvard Medical School : Director of the Fifth Surgical Service and Sears Surgical Laboratory, Boston City Hospital

IT IS IMPOSSIBLE for me to begin this lecture without a word of affectionate tribute to your great President. His generous hospitality and kindly interest when I first visited England nearly twenty-five years ago were for me the first movement in a reciprocating chain reaction which has forged many bonds of personal friendship. I had been told of the value of these friendships by my chief, the late Elliott C. Cutler. Like his chief, Harvey Cushing, he regarded them as guarantors of an intellectual exchange between our countries which would assure us of medical leadership in peace and in war. Your President introduced me to the real meaning of this exchange in a tangible and enduring way for which I am deeply grateful.

I wish Elliott Cutler could be with us today. If he could step down from Mt. Olympus, he undoubtedly would put his arm around me in his characteristic manner and say, " Don't take this too seriously. They are not half as interested in wound healing as you think they are. These awards are based mostly on friendship." And I would be more than happy to settle on a fifty-fifty basis.

However little deserved, I remain deeply sensible of and grateful for the honour which the award of a Moynihan Lecture bestows on me and on my Universities. I use the plural because when I accepted the invitation of your President, I was a member of the Faculty of Harvard University and today, as I deliver my lecture, I am from the Faculty of the University of Oregon Medical School. Such unexpected changes in one's personal life are in keeping with the fever of our times. The world is evolving at a rate which only a few years ago would have seemed impossible. Particularly is this so in fields of scientific endeavour. Surgery, which we all recognize as a science as well as an art, is no exception. Today, every body cavity can be laid open to the most minute and exhaustive explorations. Every organ can be removed or repaired and in many instances tissues can be removed, repaired and reinserted or replaced by some prosthetic device. Yet in the midst of this remarkable progress we remain painfully ignorant of the nature of the healing process itself. Despite the paucity of our knowledge, it is to this subject that this lecture is directed.

* Present Address: University of Oregon Medical School, Portland 1, Oregon.

It is fitting that the healing wound should be the subject of a Moynihan Lecture. Moynihan laid great emphasis on care and gentleness in the handling of the surgical wound. He had a great respect for tissues and for the surgeon who handled them gently, as he stressed in his Murphy Oration. Indeed, he spoke of " caressing tissues " rather than handling them. Although he wrote extensively on the care of gun shot wounds, Moynihan was not deeply interested in the " how " or " why " of tissue repair. As usual when one considers the fundamental nature of biological processes of interest to the surgeon, the earliest sound contributions are to be found in the writings of John Hunter. Hunter was profoundly interested in the fundamental nature of repair. He wrote extensively on wounds and, considering that he worked in almost total ignorance of cellular pathology, his observations were remarkably prophetic. He described healing by first intention and made a sharp distinction between what he called " adhesive inflammation " in contrast to " suppurative inflammation ". He also distinguished between the role of granulation tissue and that of the new cutis or epithelization. He clearly described the process of contraction and recognized that it occurred more readily in a rectangular wound than in a circular wound. He thought, however, that contraction was a direct result of the contraction of granulations, the same mistake which Carrel made on similar grounds one hundred and fifty years later.

Since the time of John Hunter, the most extensive explorations and excavations in the field of wound healing have mined a mass of material, only a small portion of which can be regarded as pure gold for the surgeon. For this reason I have sifted out, somewhat crudely perhaps, those aspects of our present understanding of the nature of repair which are of particular interest to the surgeon although not all of immediate practical importance. At the outset I wish to pay tribute to British workers in the period immediately after World War II. At a time when your facilities were limited, and large sums were not available for extensive projects, critical and brilliant work into the fundamental nature of repair came from your country. It is a happy circumstance that ideas are not a budgetary item and that the quality of scientific investigation is not dependent upon the gleam of the laboratory benches.

The components of repair

The repair of tissue after injury is a remarkably specific biologic reaction. It is directly related to both the nature and extent of the injury, the capabilities of the surviving tissue and the species of animal wounded. It is only in recent years that investigators have realized the necessity for considering epithelization, contraction, connective tissue growth and the final restoration of specialized tissues as distinct although interrelated biological processes. Failure to make these distinctions has led to considerable

confusion in the past. For example, it has been shown that the administration of excess thyroxin retards the gain in tensile strength of a closed wound, but the administration of thyroid extract accelerates the contraction of an open wound. Irradiation of an open wound retards contraction without affecting the formation of connective tissue as far as can be determined by present techniques. Conversely, in scorbutic animals collagen synthesis may be impaired at a time when contraction of the wound still proceeds at a normal or nearly normal rate.

In the treatment of the surgical wound such distinctions must also be made as I shall point out later.

Epithelization

The importance of species specificity is illustrated in epithelial repair. The classical pictures of epithelial coverage of a wound depicted in most textbooks of surgery are derived from studies in invertebrates such as amphibia. Paul Weiss (1959) has shown that under these circumstances epithelium rapidly migrates across the defect to unite directly with the growth from the opposite side (Fig. 1). Similar epithelial changes occur

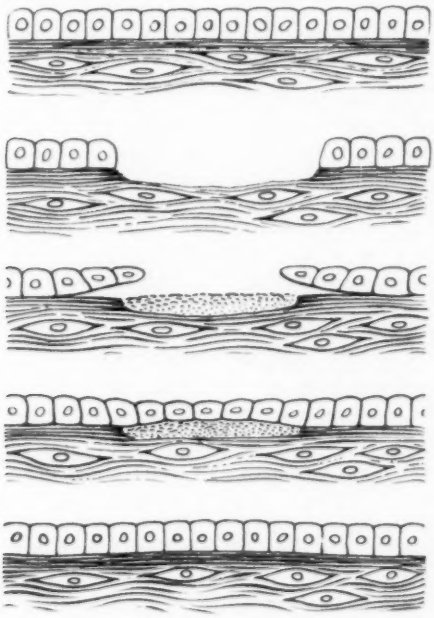

Fig. 1. Epithelial closure in amphibian skin. Note detachment and migration (after Weiss).

in tissue culture. In man, however, the process is far more complex as shown by the observations of Hartwell (1955) and Gillman *et al.* (1955). Epithelium migrates inwards over the dermal connective tissue until it comes in contact with deeper structures, at which point it undergoes considerable hyperplasia and thickening suggestive of the irregular invasive pattern of neoplasia (Fig. 2). The connective tissue-epithelial

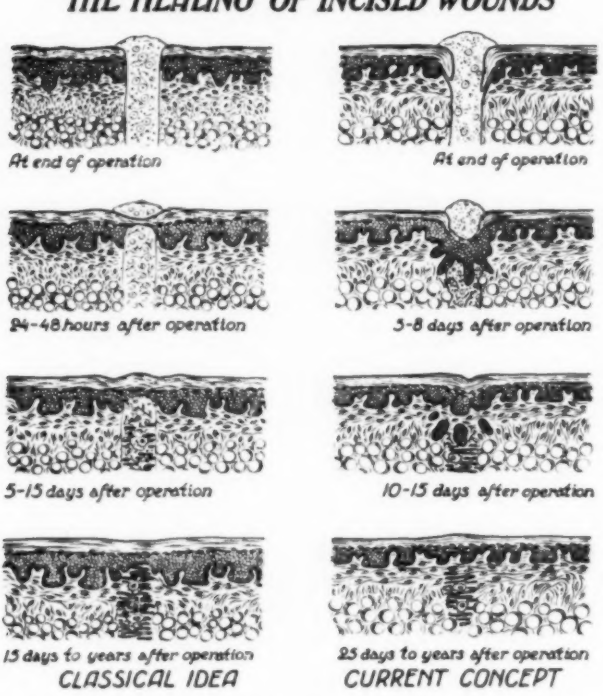

Fig. 2. (*a*) Erroneous but classical idea of epithelial closure of wound in man. (*b*) Current concept. Note migration of epithelium over dermal connective tissue and irregular pattern in depths of wound (after Gilman).

interphase is by no means distinct as is shown in this slide of some studies by my associate, Dr. Leon Edwards (Figs. 3 and 4). Note the tongues of epithelial tissue plunging in between the cells of the newly formed connective tissue. This is in a twelve-day open wound in the rat. It is only later in repair, after collagen fibres appear, that the epithelium regresses and is rearranged in a more normal pattern.

Gillman has suggested a causal relation in this sequence, and I personally cannot avoid the feeling that in this cellular interplay we are looking at the initial phases of neoplastic invasion. It is of interest that the regression of hyperplastic epithelium in a normal wound is remarkably similar to that which occurs in the regression of carcinoma of the breast under the influences of oestrogenic hormones. Similarly, in the regression

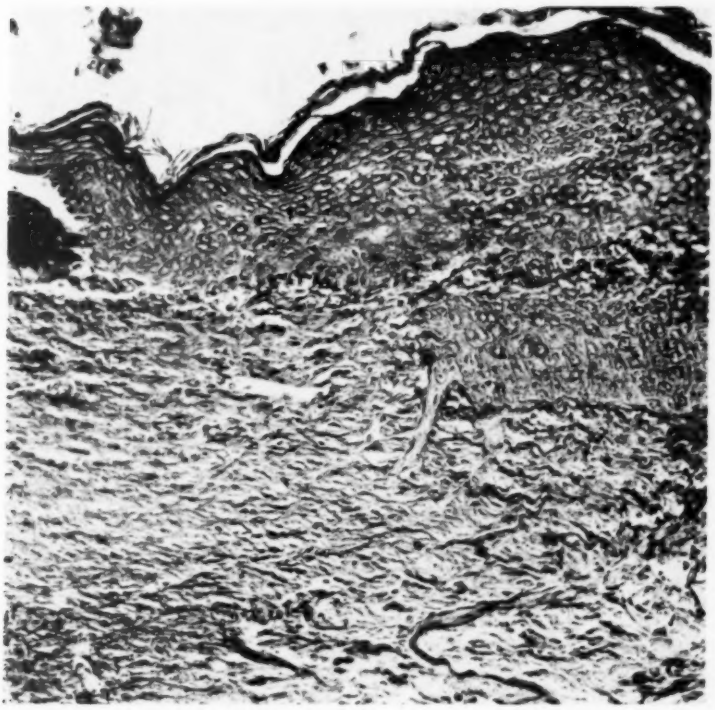

Fig. 3. Photomicrograph of a twelve-day open granulating wound. Note irregular epithelial connective tissue interface. (× 195.)

of polyps of the colon, after subtotal colectomy and ileorectal anastomosis, the epithelial re-alignment transpires without cellular necrosis (Dunphy *et al.*, 1959). Practical application of these observations at the moment rests largely in the implication that in neoplasia we should look, not only at changes within the malignant cell, but also for defects in the connective tissue stroma surrounding it. While only an hypothesis at the moment, it is deserving of extensive exploration.

Contraction

It is essential that the surgeon should recognize contraction as distinct from cicatrization. Contraction is a natural process by which the open soft tissue wound closes. It is, indeed, a form of tissue migration since very little new tissue is produced and the movement is independent of the production of connective tissue in the centre of the wound. It is a well

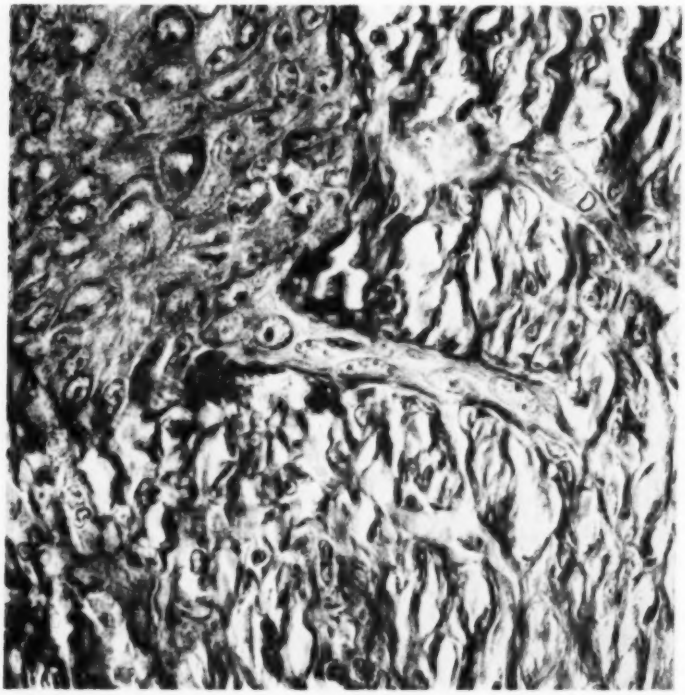

Fig. 4. High power view of Fig. 3. Epithelium is trapped amongst connective tissue cells. Regression occurs without necrosis or inflammation. (· 625.)

known clinical observation that in man contraction is most marked over the back, the back of the neck, the buttocks and the abdomen. It is restricted over the arms and legs, limited over the anterior chest wall and does not occur in circumferential wounds of the extremities. Both experimental and clinical observations confirm the fact that the burn wound contracts poorly although it scars excessively.

One must make a clear distinction between *contraction*, which is a normal physiological process without scarring, and *contracture*, which is the end

result of scar tissue formation with limitation of motion. The nature of the contractile forces in the healing of an open wound has been the subject of extensive study in recent years (Billingham and Russell, 1956; Abercrombie *et al.*, 1956; Van den Brenk, 1956; Grillo *et al.*, 1958; Watts *et al.*, 1958; Cuthbertson, 1959). There is now ample evidence to show that contraction is not synonymous with cicatrization of collagen fibres (Abercrombie *et al.*, 1956; Van den Brenk, 1956; Grillo *et al.*, 1958; Watts *et al.*, 1958). The exact force which brings about contraction of a wound is not known, but it appears to reside in a narrow edge of tissue around the periphery of the wound. It is not dependent upon the contraction of the collagen fibre nor is it related to the absorption of water or fluid from the granulation tissue. It is of interest that regeneration of the hind limb of the newt is prevented by denervation. This observation led us to suspect that neurogenic factors might affect contraction of the wound. Recent unpublished studies in our laboratory by Mr. Ian Ranger (1959) of Middlesex Hospital show no difference in the rate of contraction of open wounds on intact and denervated hind limbs of the rabbit.

The healing of special tissues

A discussion of repair in special tissues is not within the scope of this lecture nor am I properly equipped to review it with you. At the risk of making a false generalization, however, I suggest that the initial repair after injury in specialized tissues is by connective tissue. If approximation of tissues is poor and an excessive amount of connective tissue is formed, the end result is a scar. If approximation following injury is accurate so that the amount of connective tissue formed is limited, regeneration of the special tissue occurs. The available evidence suggests that in skeletal muscle this is by replacement of the connective tissue. In the healing of tendon and fascia, however, this may be a process of differentiation whereby the collagen fibres of connective tissue become re-aligned and altered so as to be indistinguishable from the special tissue involved. There is considerable evidence that function and use of the part play a role in differentiation, particularly in the healing of bone and tendon. It is quite likely, as I shall indicate later, that this is true also for fascial repair.

There is a subtle distinction which may be made here in support of the contention of John Hunter that healing by " primary intention " is different from healing by " adhesive inflammation ". Healing by " primary intention " implies such accurate approximation that regeneration of a special tissue occurs. When there is sufficient connective tissue formation to prevent regeneration but primary closure has been affected, we can say that healing is by " adhesive inflammation ". I think this distinction would please Hunter although this degree of approximation and per-

fection of repair, particularly with reference to regeneration of muscle, is probably seldom achieved surgically. It is an ideal objective.

The role of connective tissue in repair

Connective tissue became the focus for intensive study with the inception of cellular pathology. It is amazing how similar to modern discussions are the arguments regarding the nature, composition and function of connective tissue to be found in Paget's lectures on surgical pathology. Paget's concept of the development of fibrocellular connective tissue through nucleated cells in a medium of " lymph " is quite in accord with current concepts. He considered the granulation tissue as a sort of nucleated blastema similar to the blastema in limb regeneration, a view which is still worthy of careful consideration although there is some evidence against it today.

The major contributions of surgical interest which have been made to our understanding of wound healing since Virchow and Paget rest with methods of quantifying the rate of repair and the appraisal of factors which affect it. Carrell's mensuration of the open wound was an important contribution, but for mensuration of growth in connective tissue substantial credit must be given to Howes, Scoy and Harvey (1929).

Tensile strength

Our understanding of the quantitative aspects of connective tissue repair began with the studies of Howes and Harvey on the gain in tensile strength of sutured wounds. Despite difficulties in the method and some confusion in interpretation, this is a fundamental tool which remains of the greatest interest to the surgeon. Most of the confusion in tensile strength studies stems from failure to recognize the specificity of repair. The rate of gain in tensile strength differs substantially in different tissues, in different species and at times in the same tissues in the same species. These differences may be substantial. Methods of testing also introduce sizeable errors. Despite these drawbacks, much has been learned from studies of tensile strength.

Regardless of the tissue studied or the method employed, there is a delay between wounding and the onset of a rapid gain in tensile strength. This delay varies. When the whole wound is studied, as in the abdominal wall or the gastric wall, the significant gain in tensile strength appears between the fourth and sixth day. When fascia alone is tested, a substantial increase in tensile strength does not appear until the sixth or eighth day.

In the classic studies of Howes *et al.* (1929), and in most studies of the intact wound, it has been assumed that maximal strength of the wound was reached at approximately fourteen days. However, more

recent studies of repair in the skin and subcutaneous tissue as well as tendon and fascia indicate that there is a second phase of gain in tensile strength which may last for long periods of time (Howes *et al.*, 1939; Mason and Allen, 1941). In tendons this is clearly related to function and probably represents the process of differentiation whereby connective tissue cells assume the properties of fascial or tendon cells. The studies of Douglas suggest that this process may not be complete for nearly one year and even at that time the wound has not attained the strength of intact normal fascia (Douglas, 1952) (Fig. 5).

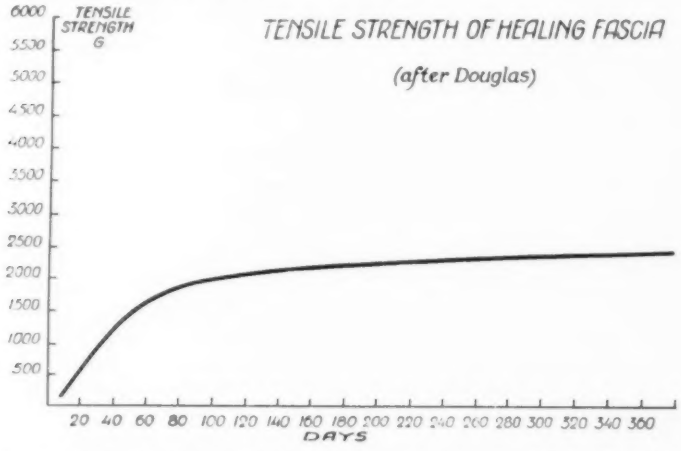

Fig. 5. Rate of gain in tensile strength of sutured aponeurosis (after Douglas).

The use of tensile strength as a measure of the rate of repair has permitted extensive explorations of factors which delay or alter repair, particularly depletion of vitamin C and proteins. Of even more interest to the surgeon, of course, are measures which might accelerate repair and shorten the so-called lag phase between injury and the onset of a gain in tensile strength. Despite much work there is no clear-cut means as yet by which this period can be shortened.

The delay in gain in tensile strength following injury was regarded by Harvey as a lag phase, primarily related to demolition or reorganization in the wound. I prefer to think of this phase as a preparative rather than a lag phase, because under ideal circumstances fibroblastic activity begins very quickly after injury and proceeds *pari passu* with absorption and demolition of injured cells. The more one studies the repair of tissues after injury, the more it appears to be one continuous cellular process. Fibroblasts appear within twenty-four to forty-eight hours of injury and minute amounts of collagen can be detected by histochemical analysis.

It is quite possible that were we able to measure tensile strength more accurately, a progressive increase from the very earliest phases of healing could be demonstrated.

Nevertheless the concept of a lag phase in wound healing, although not biologically correct, is of vital importance to the surgeon because it is during these days that the strength of the wound is confined largely to that provided by the sutures plus the initial gelation of the wound, Hunter's adhesive inflammation. For this reason, for generations surgeons have been intrigued with the hope of hastening repair. Thousands of topical agents have been alleged to produce more rapid healing, but careful quantitative studies indicate that such agents merely restore impaired healing to normal. The idea of wound hormones persists, however, and there is substantial evidence that systemic factors are important in the repair of wounds in plants.

Some years ago Philip Sandblom thought he found evidence of systemic wound hormones in animals (1944). His earlier studies suggested that a wound made approximately ten days after a previous wound in some other part of the body healed more rapidly. We were unable to confirm this observation (Savlov and Dunphy, 1954a and b), but there is undoubted evidence that the resutured wound heals more rapidly than a fresh primary wound (1954b). This observation has been confirmed by Sandblom and Muren (1954). The very careful studies of Douglas (1959) leave no doubt that there are important local healing-promoting factors in repair. In our studies of the fascia, muscle and peritoneum as a unit, the healing-promoting phenomenon was maximal at five days and progressively declined for a period of about forty days. Douglas, testing fascia alone, found the maximal healing-promoting effect at twenty-one days. In his studies also the effect persisted for about forty days.

The exact nature of the local rehealing phenomenon is not understood. The studies of Prudden and his colleagues (1957) suggest that the preparatory phase of repair may be shortened by introducing powdered cartilage into the wound. His more recent studies show, however, that although there is greater coagulability and a slightly increased tensile strength at five days, ultimate repair, as judged by maturation of connective tissue, is delayed—a result which might have been predicted on the basis that the cartilage acts as a foreign body (Paulette and Prudden, 1958).

An attempt to evaluate the nature of the local rehealing phenomenon has led us to a study of the biochemistry of the factors which contribute to tensile strength.

Fibrogenesis and the formation of collagen

It now appears likely that the tensile strength of a wound is related, not only to the rate and extent of fibroblastic proliferation, but also to the

ability of the fibroblasts, together with other factors, to produce a normal collagen fibre. The extensive investigations of the relation between fibrogenesis and collagen formation have been reviewed recently by Jackson (1958). Only the highlights will be outlined here.

A hypothetical model of some of the factors in fibrogenesis is shown in Figure 6. The origin of the "primary connective tissue cell" is still un-

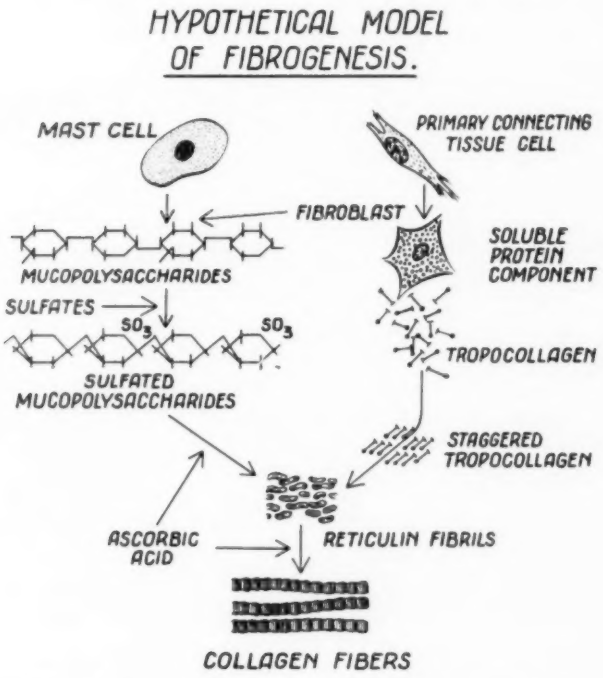

Fig. 6. A hypothetical model of some of the factors which contribute to the formation of collagen in the healing wound.

settled. It probably varies with the site of injury. There is considerable evidence indicating that cells from loose areolar tissue participate in the repair of fascia and muscle, a point of considerable surgical importance. Hartwell has stressed this and our own observations are in accord with this view. One point appears certain. Organization of the wound proceeds from the periphery. This is well shown in Figure 7, which shows fibroblastic proliferation in the interstices of a plastic sponge. The peripheral organization is obvious. In Figure 8, taken from some unpublished studies of Dr. Leon Edwards, it can be seen that the dermal connective

tissue does not participate in the repair of subcutaneous tissue. It remains inert while the new cells appear to be sweeping up into the wound from the areolar tissue above the fascia. From a practical surgical point of view, these observations stress the importance of not damaging the areolar tissue and fat. Wide dissection of fascial planes would seem to be not only unnecessary but biologically deleterious.

Just how the young connective tissue cells produce fibres has been a subject of controversy since the introduction of the microscope. The

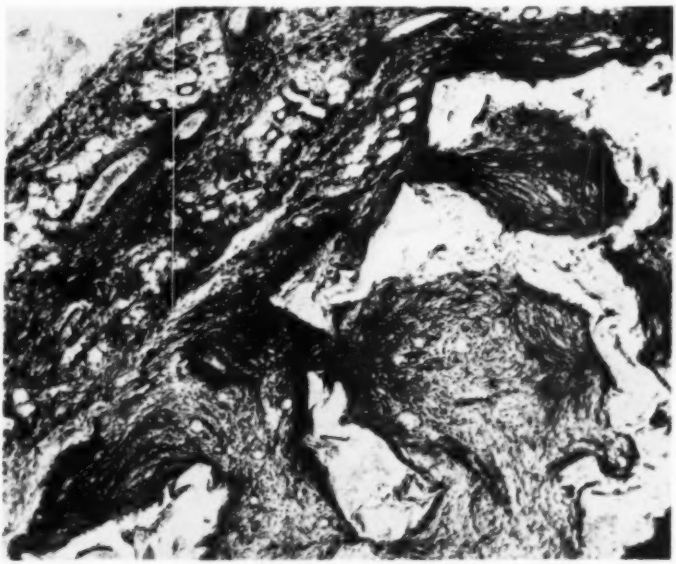

Fig. 7. Photomicrograph showing growth of connective tissue in the interstices of a plastic sponge. The organization proceeds from the periphery. Hale's and Van Giesen's stain. (× 327.)

principal argument has settled around whether or not the fibre arose from the cell or from intercellular materials. Although the factors which contribute to fibre formation and influence it favourably or unfavourably may be extracellular, the process itself appears initially to be an intracellular phenomenon. As shown in the diagram (Fig. 6), the cell produces a soluble protein component which may have the chemical composition of the collagen fibre within the cell. Upon leaving the cell this material, which is basically a long chain polypeptide, becomes a relatively rigid rod about 3000 A. long and 50 A. in cross section. These so-called fibres of " tropo-collagen ", under the influence of environmental factors

in the ground substance or intercellular material, are aligned in a staggered position and fuse to form typical adult collagen with an axial striation of 640 A.

The solubility of the collagen fibre is a function of the number of chemical bonds between rods. With increasing age the binding of these units one to another is increased. Hence, variabilities in the solubility of collagen occur although the basic chemical composition appears to be essentially the same.

The role of mucopolysaccharides and sulphates in the formation of collagen has been the subject of considerable controversy. It is clear that

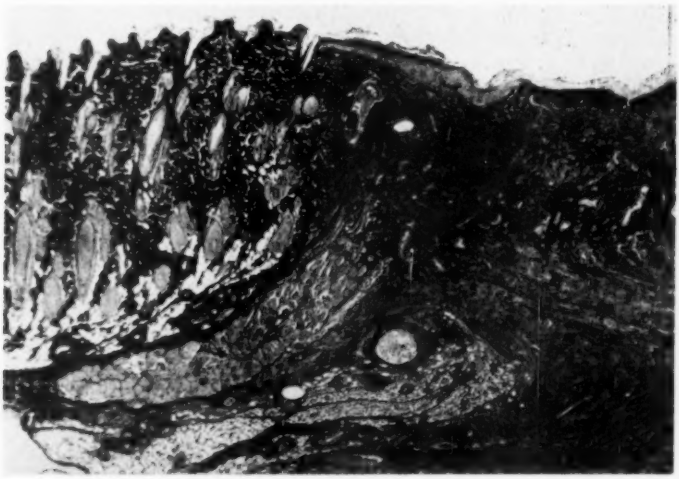

Fig. 8. Photomicrograph showing growth of connective tissue in a twelve-day wound. Note that the dermal connective tissue appears inert. Proliferation is from the loose areolar tissue in the depth of the wound. Hale's and Van Giesen's stain. (× 135.)

the physical state of collagen fibres from adult soluble collagen to the earliest stage of extractable soluble collagen can be effected *in vitro* without the presence of mucopolysaccharides. *In vivo*, however, the altered histochemical staining reactions of young connective tissue have led to the postulate that polysaccharides in the intercellular material or ground substance provided a medium that is specific for collagen formation. On the basis of such staining reactions and the quantitative measurement of hexosamines in the healing wound, a pattern typical of biochemical sequences in normal connective tissue growth was derived (Dunphy and Udupa, 1955).

More recent studies, using chemical techniques specific for polysaccharides such as chondroitin sulphate, indicate that this material is not produced in the wound in significant amounts prior to or during the period in which collagen fibres are forming (Jackson and Dunphy, 1960). The relative chemical composition of the healing wound with reference to hexosamines, the specific mucopolysaccharide, chondroitin sulphate and collagen is shown in Figure 9. The concentration of hexosamine falls

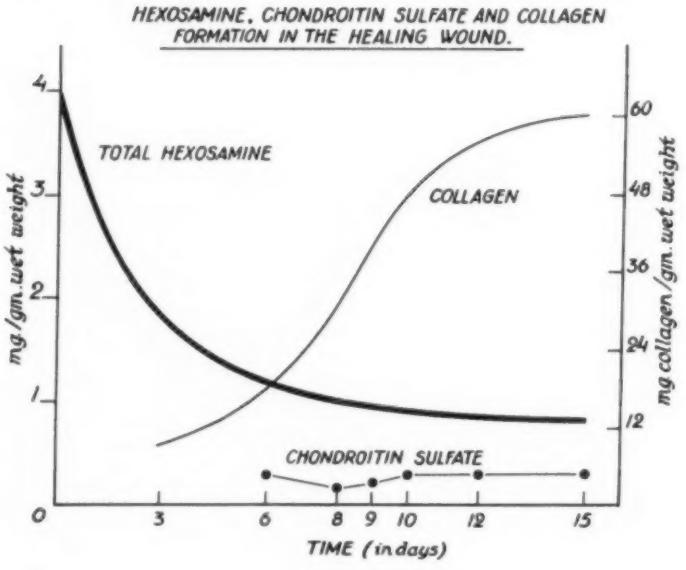

Fig. 9.

progressively from the time of wounding, suggesting that these materials are a component of the exudate in the wound. Collagen appears early and its concentration parallels the familiar curve of gain in tensile strength. There is little or no change in chondroitin sulphate although, towards the end of the healing period, this material rises to levels comparable to that found in normal skin. This does not mean that polysaccharides in the ground substance do not play a role in the alignment of the collagen fibre, but it does show that an abundance of this material is not produced in the wound during the early stages of repair and reabsorbed later.

It seems quite likely that tensile strength is a function not only of fibroblastic proliferation but of the production of normal collagen. Whether or not the second phase in gain in tensile strength described by Howes, Mason and Allen and Douglas is related to an alteration in the

solubility of collagen is not known. It would be in accord with the present views, however, regarding the nature of young and old collagen. With the passage of time as collagen ages and bonds between collagen fibres increase in number, one can conceive of a tougher, more resistant, less soluble collagen, which has a greater tensile strength than young collagen. The influence of use and function on the physical state of collagen fibres is a problem meriting evaluation.

Abnormal connective tissue repair

Although little is known about methods of accelerating the rate of connective tissue repair beyond the normal, there are many factors which delay repair. Some of these are specific for connective tissue repair alone and others retard all components of the repair process. Some specific situations which impair connective tissue repair are a deficiency of ascorbic acid, protein starvation, methionine deprivation and the administration of massive amounts of cortisone.

There are significant and measurable differences in the manner and extent to which these various factors influence repair. For example, a lack of ascorbic acid appears to block the formation of collagen fibres at the points shown in Figure 6 (Dunphy *et al.*, 1956). Protein starvation, on the other hand, slows all phases of repair, but what collagen is formed is apparently normal (Udupa *et al.*, 1956). Cortisone in large doses decreases the formation of collagen, but its action is very complex. For example, it has no effect if it is given after the healing process has been initiated. The effect of cortisone is abolished by adrenalectomy even though the doses of cortisone are far in excess of the physiological amounts which would be produced in ordinary stress (Pernokas *et al.*, 1957). No satisfactory explanation for the mechanism of action of cortisone on collagen synthesis has been established. It is of interest, however, that cortisone also has a direct effect on the permeability of connective tissue membranes. Thus it reduces the permeability of connective tissue to phenol-sulphophthalein and prevents the lytic effect of hyaluronidase. It is possible, therefore, that the effect of cortisone on connective tissue cells may be by interference with nutrition through the blockage of transfer mechanisms in the intercellular substance.

The tensions of the nuclear age have focused interest on the effects of total body irradiation on repair. There is considerable evidence to show that immediately after whole body irradiation, healing proceeds at a normal or nearly normal rate with respect to contraction, gain in tensile strength and the formation of collagen. With massive doses, 600 r, collagen formation is significantly impaired at eight days but rises to the normal range by sixteen days (Flickinger *et al.*, 1959).

These experimental observations would indicate a need for prompt closure of wounds in nuclear warfare since healing is known to be adversely affected in the later stage of irradiation illness.

Despite obvious measurable differences in the deleterious effects of various mechanisms on repair, there is a growing body of evidence that the final defect is some form of cellular privation. Even the effect of ascorbic acid deficiency which has in the past been thought to be largely extracellular in action, now appears to be related in part at least to starvation.

The effect of bacterial pyrogens on connective tissue

John Hunter suggested that injury differed from disease in that it had in all cases a tendency to produce both the disposition and the means of cure. The role of fever in this situation may be significant. The effect of bacterial pyrogens has been studied of late in a host of conditions and has been shown to increase resistance to infection, to reduce the size of malignant tumours and to favour healing in wounds. The evidence for this latter observation is somewhat tenuous.

Recently we have been exploring the effects of bacterial pyrogens on connective tissue repair. A relatively small amount of pyrogen will produce striking changes in the carrageenin granuloma. There is a marked increase in size of the granuloma, a heavy infiltration of leucocytes and an increase of collagen production. This occurs without suppuration. One cannot avoid the influence that this is a classic example of the adhesive inflammation of Hunter's. Whether or not this will be shown to be beneficial and whether or not it will lead to accelerated repair is quite another matter, however. Some preliminary studies of the effects of a bacterial pyrogen (*E. coli*) on the production of collagen in implanted polyvinyl sponges in guinea pigs indicate that, under these circumstances, it also promotes a more rapid formation of collagen.

Some practical conclusions

One may well ask what conclusions of practical significance can be drawn from the mass of information which has accumulated about the nature of the healing process. There are several, some old, but often forgotten, and others new.

First is the vital importance of distinguishing between the various components of repair and the factors which influence them. Particularly must the surgeon recognize contraction as a physiological process of great usefulness if the wound is on the back of the neck, the back, the abdomen or the buttocks. The experimental evidence indicates that exposure of large soft tissue wounds in these areas should hasten closure. Although conclusive evidence from the clinic is lacking on this point, the very rapid closure by contraction of perineal and perianal wounds where dressings

rarely can be kept in place justifies a clinical trial of exposure of other soft tissue wounds. The essential point about contraction is that it renders skin grafting unnecessary and allows closure without extensive scarring. On the other hand, it must be remembered that burn wounds contract poorly and, hence, must be grafted early. This is true also of wounds over the extremities—the hands and feet, the anterior chest wall and the anterior neck. Of course, with multiple large wounds as in warfare, early grafting may be necessary simply to accomplish early closure. The split skin graft is ideal for this purpose because, although it slows, it does not abolish contraction. Large wounds will continue to contract and graft can be excised and primary union brought about at some later date.

With regard to epithelization, the curious downward growth of epithelium which occurs in primary wound closure, although not of immediate practical importance, should stimulate an investigation of the role of this phenomenon in neoplasia.

The role of fibrocytes which come from loose areolar tissue in the repair of wounds of fascia and muscle make it desirable to avoid a wide dissection and isolation of fascia or muscle when possible. For this reason it does not make sense to overlap or imbricate fascia. This has been confirmed by a recent experimental study which indicates that overlapping of fascia not only does not lead to an increase in tensile strength but, on the contrary, particularly if the overlap is excessive, weakens the wound (Farris, 1959).

There are several points in regard to the gain in tensile strength of wounds which merit emphasis. Most surgeons are aware of the classic curve of gain in tensile strength with its initial delay and rapid rise to an apparent peak at about fourteen days. Many, however, are not cognizant of the second phase of gain in tensile strength characteristic of all wounds, but particularly important in the repair of tendons. The specific role of function in the development of tensile strength during this second phase is of great practical importance.

It is a comfort to the surgeon to know that a wound which has dehisced from mechanical stresses will heal more rapidly than a fresh primary wound. The fact, however, that this healing-promoting phenomenon of the resutured wound persists for a good month has additional implications. Provided there is no infection, reoperation through the same wound at any time during this period can properly be undertaken, particularly during the first two weeks after operation. I have made personal use of this in operating for unexpected early complications of major abdominal surgery. The initial wound can be reopened rapidly without bleeding and heals remarkably well. If reoperation is performed between five and ten days postoperatively, the resutured wound should have nearly the same tensile strength as it would have had if reoperation had not been necessary.

Most surgeons are aware of the deleterious effects of protein and vitamin C deprivation on wound healing. The significant relation of these factors to the time of wounding, however, is not always appreciated. If there are no deficiencies at the time of wounding, repair will proceed normally despite deficiencies in the immediate post-injury period. Conversely, however, if the wound is made prior to the correction of deficiencies, corrective measures taken in the post-wounding period are much less effective. This merely stresses the need for correcting specific deficiencies prior to operation if possible.

One further point should be mentioned with regard to ascorbic acid deprivation. There is a remarkable demand for ascorbic acid by the body following severe stress, and since ascorbic acid appears to be utilized and metabolized in the repair process, it should be given liberally following operation even though there are no specific deficiencies. A specific requirement has not been established, but in the light of present knowledge in cases of severe injury with multiple wounds, a dosage of 500 to 1,000 mg. would not be excessive.

The experimental evidences indicate that, immediately after total body irradiation, healing is likely to be normal. Later, it may be impaired because of bleeding from hypoprothrombinaemia. Consequently, wound closure should be performed as early as possible in the event of combined traumatic and nuclear injury.

Although an understanding of the biochemical aspects of fibrogenesis and the specific role of collagen in providing tensile strength to the wound is of less immediate practical importance to the surgeon, the time has come when he must be aware of this aspect of repair. It seems likely that any progress towards shortening the normal rate of wound healing will depend on a better understanding of fibrogenesis and the formation of collagen. The possibility of precipitating the preparative phase of the repair process without actually making a wound must not be overlooked. It would seem to be within our scope.

In closing, I am forced to admit that two centuries of inquiry into the nature of the healing process has brought us but a very little way beyond John Hunter, but this fact must not weary us. Consider the advice of Iago to the discouraged Roderigo—

> " How poor are they that have not patience!
> What wound didst ever heal but by degree?
> Thou know'st we work by wit, and not by witchcraft?
> And wit depends on dilatory time."

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PRIMARY FELLOWSHIP EXAMINATIONS OVERSEAS

IN RESPONSE TO requests from the University of Ceylon and the University of Khartoum, a party of examiners was sent by the Council in January to conduct Primary F.R.C.S., Primary F.D.S., R.C.S. and Primary F.F.A., R.C.S. examinations in Colombo and, for the first time, a Primary F.R.C.S. examination in Khartoum. The examiners from this country were Mr. J. Basil Hume, F.R.C.S., Professor D. V. Davies, Professor Robert Knox, Professor E. A. Park, F.F.A.R.C.S., and Professor G. L. Roberts, F.D.S.R.C.S., Professor A. C. E. Kock of the University of Ceylon and Professor Dean Smith of the University of Khartoum examined in Physiology at their respective centres.

The numbers of successful candidates were as follows:

In Ceylon

Primary F.R.C.S. Examination	.. ..	16 out of 85
Primary F.D.S. Examination	.. ..	4 out of 29
Primary F.F.A. Examination	.. ..	2 out of 5

In Khartoum

Primary F.R.C.S. Examination	.. ..	4 out of 11

NON-MALIGNANT BILE DUCT OBSTRUCTION

Hunterian Lecture delivered at the Royal College of Surgeons of England

on

26th February 1959

by

Cyril Havard, M.Ch., F.R.C.S.

Senior Surgical Registrar, Cardiff Royal Infirmary

IT MUST BE a rare occasion when someone, interested in a particular clinical problem, turns unavailingly to the recorded works of John Hunter, such was his wide interest in biological phenomena. The diversity of his interests, as compared with the present day trend towards increasing specialization, is the more surprising in view of the detailed observations he made on so widely differing subjects. His observations on the functions of the liver and biliary duct system were no exceptions. These included the effects of obstruction to the gall bladder by a stone impacted in the cystic duct and he was interested to note that " the gall bladder was very much contracted although not diseased, and its contents were a pellucid slimy mucus, not in the least tinged or bitter to the taste ".

The passage of time and improvements in techniques in operations on the biliary tract have done nothing to prevent the incidence of gall stones and they remain as dangerous today, untreated, as they were in the days of John Hunter. The incidence of stones in the bile ducts, overlooked at operation, is, however, in great part preventable and this lecture is intended—one, to discuss the problems of the overlooked duct stone and methods for its prevention, and

—two, to describe some of the ill effects on the liver caused by duct stones, overlooked or otherwise.

THE PROBLEM OF THE RESIDUAL DUCT STONE

The incidence of stones in the bile ducts and its relation to the proportion of ducts explored

The frequency with which duct stones are reported to occur in calculous biliary tract disease varies widely from one authority to another. Crump (1931), reporting on routine post mortem examination of 1,000 patients, found stones in the bile ducts in a quarter of those patients with calculous disease of the biliary system. This figure, which is supported by the findings of Maingot (1948), is far different from such figures as 6.8 per cent. as quoted more recently by Glenn (1952).

Table I shows how, at the United Cardiff Hospitals, between 1946 and 1954 at the Cardiff Royal Infirmary and between 1942 and 1954 at Llandough Hospital, 702 patients underwent primary operations for calculous biliary tract disease, 148 having their ducts explored, an exploration rate of 21 per cent. Of these, 84 were found to have stones in the ducts, an incidence of 12 per cent.

This falls between the figures given by Crump (1931) and Maingot (1948) and those given by Glenn (1952) and, in an effort to explain these differences, a comparison has been made between the percentages of ducts explored and the incidence of duct stones, given as a percentage of the

TABLE I

INCIDENCE OF STONES FOUND IN THE BILE DUCTS

Cholecystectomy	518	554 (78.9 per cent.)
Cholecystostomy	36	
Choledochostomy with cholecystectomy	139	
Choledochostomy with cholecystostomy	4	148 (21.1 per cent.)
Choledochostomy only	5	
Stones found		84 (11.9 per cent.)
No stones found		64 (9.1 per cent.)

total. The incidence of stones has been plotted against the frequency of duct exploration, using the data already mentioned together with other figures taken quite at random from the literature.

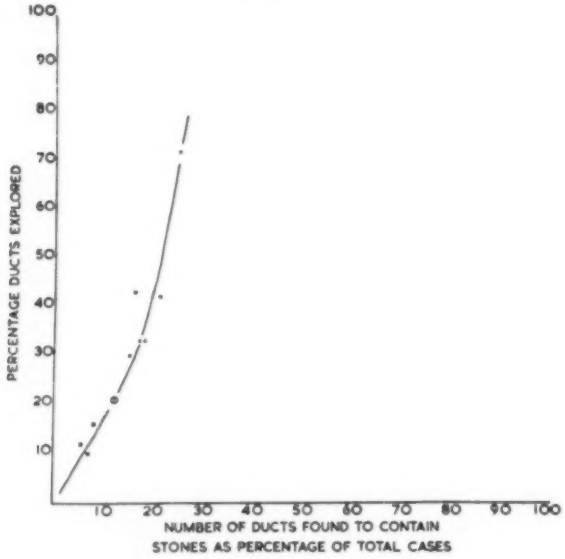
The graph thus produced in Table II demonstrates well the direct relationship of the incidence of stones found in the ducts to the rate of duct exploration.

Study of these figures implies that, taking the overall incidence of bile duct stone to be roughly constant, the surgeon who explores the lesser number of ducts, though he finds stones in more of the ducts he *has* explored, should have the higher incidence of residual stones because of the ducts he has left alone. The exploration rate of 21 per cent. and the incidence of duct stone in 12 per cent. in this series, shown by a ring, are appreciably lower than several of the other figures quoted and thus a correspondingly higher incidence of residual stones might be expected. In theory, if the actual incidence of duct stone is 25 per cent., one would expect an incidence of residual stone in the region of 12 per cent.

The incidence of stones in the ducts overlooked at cholecystectomy

To try and estimate the actual incidence of residual duct stones in this series, selected cases were followed up. Those patients who had nothing clinical or operative to suggest the presence of stones in the bile ducts were not followed further. Those patients known to have had bile duct stones which were treated quite uneventfully by choledocholithotomy were also discarded. Several patients had clinical histories highly suggestive of bile duct stones, but no stones were found on choledochotomy. These were not followed up, though it is possible a small number may have had overlooked stones.

TABLE II



This left a group of patients where it was either known that stones were left in the ducts or suspicion of their presence was reasonable on clinical or operative grounds or because of the development of one of their complications.

Of the 702 patients operated on in this series, 105 *appeared* to have one or more of these indications. Of these 105 patients, 61 attended personally for follow up, a further 13 being traced by questionnaire. The remaining 31 could not be traced. The length of follow-up amongst those who attended personally is shown in Table III.

Of the 554 patients who had undergone cholecystectomy or cholecystostomy only, it was found that 40 or 7.2 per cent. had at some time been readmitted to hospital (Table IV). Eighteen of these 40 patients had been re-explored, residual stones in the ducts being found in 13 or 2.3 per cent., 12 of the patients remaining free from symptoms following the removal of the residual stones. Two of the three patients, in whose ducts *no* residual stones were found, continued to have recurrent pain and jaundice. The two remaining patients were found to have peptic ulcers.

TABLE III

LENGTH OF FOLLOW-UP DATED FROM FIRST OPERATION ON BILIARY TRACT

Length of follow up	No. of cases
1 – 3 years	21
4 – 5 ,,	17
6 – 10 ,,	18
11 – 15 ,,	3
Over 15 ,,	2
TOTAL	61

The other 22 readmitted patients were *not* re-explored but their reasons for readmission are also shown. It is interesting that indications for exploring the ducts were present prior to the cholecystectomy in those three who subsequently developed acute pancreatitis and in all those who were jaundiced at any time following their operation, and it is possible that a number of residual stones may be included amongst these cases also.

These figures show that the incidence of overlooked stones in the ducts following cholecystectomy is low—certainly low in comparison with the incidence following exploration of the ducts, as will be shown later. Of the 7 per cent. who returned with symptoms following their cholecystectomy, only 2.3 per cent. were proved to have residual stones. This figure could have been reduced almost to nil if the usual indications for exploring the ducts had been respected in every case, for it was found in 10 of the 13 cases that a history of jaundice had been present prior to the cholecystectomy, and jaundice was only considered significant when accompanied by dark urine and pale stools.

Another way of putting it is that the total incidence of stones in the ducts proved to be 13.8 per cent. and these would have been discovered if 23.6 per cent. of the ducts had been explored. These figures are still appreciably below many of those quoted elsewhere and the possible reasons are that the true incidence of duct stones may vary and that a proportion of duct stones may not give rise to symptoms.

Routine choledochotomy might seem the answer to the symptomless stones in the ducts, but the great majority of these routine explorations

proving unnecessary is likely to deter the most patient of surgeons. This is apart from the added hazard of choledochotomy for, though Lahey (1932) has claimed that the increased mortality is due to the effects of the stones in the ducts rather than to the exploration, it must be accepted that exploration of the ducts does slightly increase the risk of the operation.

TABLE IV

PATIENTS READMITTED TO HOSPITAL FOLLOWING CHOLECYSTECTOMY OR CHOLECYSTOSTOMY ONLY

Total number

554

Number readmitted to hospital

40 (7.2 per cent.)

Number re-explored		Number not re-explored	
18		22	
Proven stones	13 (2.3 per cent.)	Acute pancreatitis	3
No stones found	3	Chronic pancreatitis	2
Other pathology	2	Pain and jaundice	8
		Pain and fever	1
		Pain only	6
		Recurrent biliary discharge	2

The mortality rate in the present series was appreciably raised when the duct was explored, irrespective of whether stones were present or not (Table V).

TABLE V

MORTALITY RATE OF CHOLECYSTECTOMY WITH AND WITHOUT CHOLEDOCHOTOMY

Operation	Total number	Deaths	Mortality rate	Average age
Cholecystectomy Cholecystostomy	554	11	2%	63
Cholecystectomy with Choledochotomy Cholecystostomy with Choledochotomy	143	7	4.9%	66

Even allowing for the fact that some of these patients would have been jaundiced at operation and correspondingly poorer operative risks, these

figures of 2 per cent. and 4.9 per cent. would support the increased mortality rates of choledochotomy as reported by Grey Turner (1939), Bartlett and Quinby (1956) and others.

The incidence of residual stones in the ducts after exploration of the ducts

Is exploration of the ducts sufficiently accurate to be sure that its routine use can guarantee to find all those stones which are so small as to be symptomless and impalpable? Even when stones are present, is exploration by the usual techniques a sure means of clearing the ducts of these stones?

The difficulty of proving the patency of the sphincter of Oddi with a probe, without opening the duodenum, is already well recognised. The presence of a probe in the duct during palpation, even after partial mobilisation of the head of the pancreas, is of limited value only, for quite large stones may be missed in an obese patient if the stones are soft and friable and the pancreas thickened and indurated by infection.

Such conditions were present in an obese woman whose duct was explored and several soft, mushy stones removed. The pancreas was thickened, but a probe appeared to enter the duodenum without obstruction.

The post-operative cholangiogram (Fig. 1), however, reveals the size of stone which may be missed under these conditions by the usual techniques.

Fig. 1. A post-operative cholangiogram showing the size of stone which may be missed by the routine methods of duct exploration when the stone is of very soft consistency.

The incidence of residual stones in the ducts after choledochotomy in the present series is 13.5 per cent. and compares quite unfavourably with the incidence of stones overlooked in the ducts after cholecystectomy only.

Of course, the true incidence of residual stones will always be slightly higher than the apparent, when one takes into account the symptomless stones left in the ducts. That residual stones may lie in the ducts for long

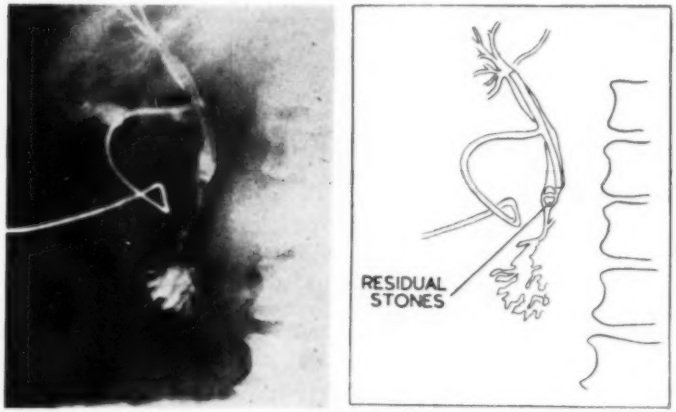


Fig. 2

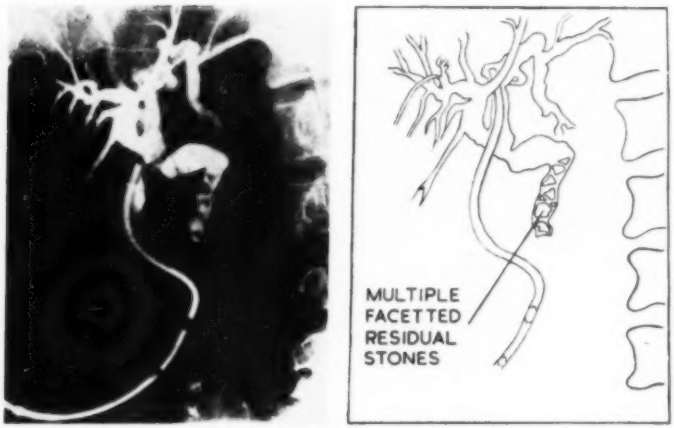


Fig. 3

Figs. 2 & 3. Post-operative cholangiograms showing residual stones in the common duct. Both patients have remained completely free of symptons for three years.

periods without giving rise to symptoms is shown by the following two cases.

The post-operative cholangiogram seen in Figure 2 shows at least two stones at the lower end of the duct, while Figure 3 shows a greater number of stones which were knowingly left in the duct because of the patient's sudden collapse on the operating table.

Both these patients, both intelligent witnesses, denied symptoms of any kind when seen at follow-up three years post-operatively.

Certainly one should not wait for the appearance of jaundice before diagnosing the presence of residual stones. A man aged 45 years was investigated because of three years' flatulence and indigestion. Though his gall bladder had been removed twenty years previously, there had been no jaundice at any time since then and a barium meal examination was carried out on the clinical diagnosis of peptic ulceration.

Figure 4 reveals the appearance of his barium meal, the indentation of the second and third parts of the duodenum being proved at operation to be due to immense dilatation of the common duct by innumerable stones.

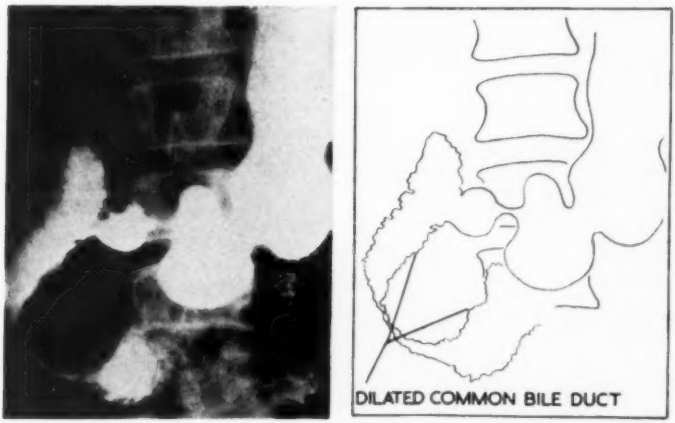


Fig. 4. A barium meal showing indentation of the duodenum caused by a dilated common bile duct containing innumerable residual stones, in a patient who had not complained of jaundice.

A side-to-side choledochoduodenostomy was performed, no effort being made to remove all the stones, and, when seen again five years later at follow-up, he had remained symptom free, still without any evidence of jaundice.

It may also be argued that the true incidence of residual stones will always be slightly *lower* than the apparent, when one allows for those

stones re-formed in the ducts. Johnston *et al.* (1954) has described four years as the average period following operation when re-formed stones begin to cause symptoms and also describes their physical characteristics as being typically soft and mushy. Knowing from the cases previously presented how long patients with definitely residual stones may remain free of symptoms, the time of onset of recurrent symptoms would seem to be of little value in the diagnosis of re-formed as opposed to residual stones. Likewise, in our experience, friable and mushy physical characteristics have appeared to be more related to the presence of duct infection—the more marked the clinical and operative evidence of duct infection, the softer the stones appeared to be.

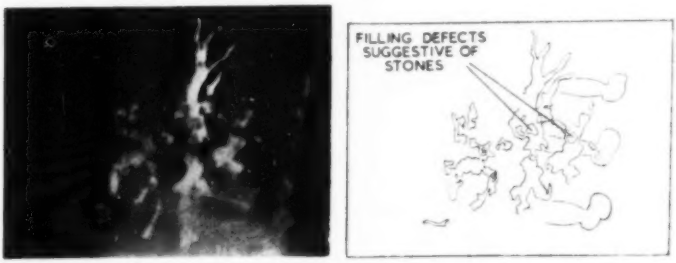


Fig. 5

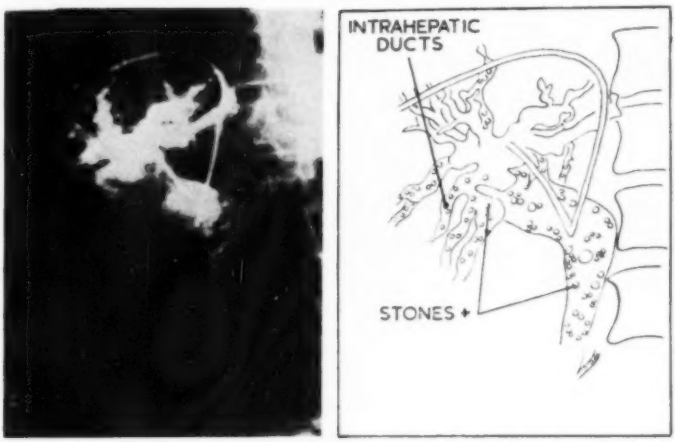


Fig. 6

Figs. 5 & 6. The post-operative cholangiogram in Fig. 5 (performed with lipiodol) shows few stones, the vast number of stones seen in the same patient six years later in Fig. 6 being explained only by the re-formation of stones in the common duct.

That re-formed stones can and do occur is now widely accepted. Only by accepting this principle can one explain the cholangiographic appearances seen in the case of a male patient aged 61 years who was admitted with a three-month history of abdominal pain and jaundice. A gall bladder containing stones was removed and stones and biliary mud removed from a dilated bile duct which was drained.

The post-operative cholangiogram in Figure 5 shows several negative shadows thought to be residual stones and although this is a poor quality cholangiogram, performed in the earlier days of the technique with lipiodol, it is obvious that there are nothing like the vast numbers of stones seen to be present in the cholangiogram in Figure 6. This was performed when the ducts were re-explored because of recurrent symptoms six years later.

The vast increase in numbers between the times of the two cholangiograms can only be explained by the re-formation of stones and it is interesting to note that the majority of the stones in the hepatic ducts are to be found in the dependent parts of the duct system where less efficient drainage predisposes to infection and calculus formation.

The use of operative cholangiography in the prevention of residual duct stones

To summarise these findings, it may be said that a comparison has been made in the same series of cases, between the incidence of residual stones in the ducts after cholecystectomy only and after cholecystectomy with exploration of the ducts (Table VI). Figures have not been used from

TABLE VI

INCIDENCE OF RESIDUAL STONES

Operation	Total number	Residual stones	Percentage incidence
Cholecystectomy Cholecystostomy	554	13	2.3%
Cholecystectomy with Choledochotomy Cholecystostomy with Choledochotomy Choledochotomy only	148	20	13.5%
TOTAL	702	33	4.2%

cases operated on after the introduction of operative cholangiography in these hospitals, so that the results are not influenced by the use of this technique.

It has been shown that the incidence of residual stones after cholecystectomy only, where no clinical or operative indication for duct exploration has been overlooked, is so negligible as to contraindicate the use of *routine* operative cholangiography. In fact the advice of Ogilvie (1957) to " Leave the common duct alone " should be respected in *these* cases. (Whether routine operative cholangiography might reduce the incidence of unnecessary and fruitless exploration of the ducts is another question and is not relevant to the present problem.) Similarly it has been shown that the incidence of residual stones following cholecystectomy with exploration of the ducts is relatively high and is, I feel, ample justification for the routine use of operative cholangiography *whenever the ducts are explored.*

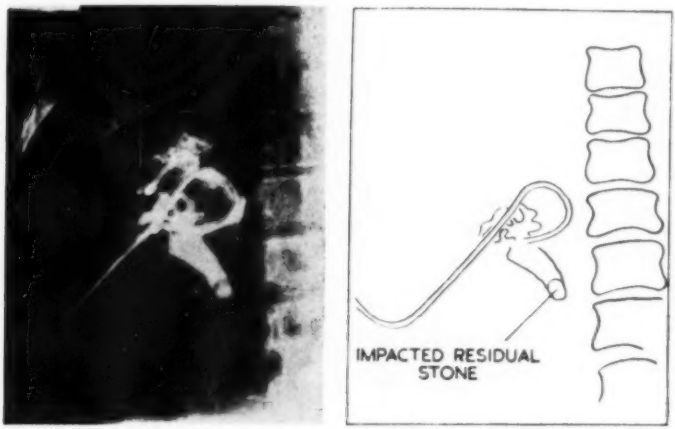


Fig. 7. A post-operative cholangiogram with complete hold-up of the dye by an impacted stone, thus concealing another large stone distally.

Stones in the hepatic ducts may be demonstrated by this method as may the free flow of dye into the duodenum. The use of operative cholangiography has the added advantage of making unnecessary post-operative cholangiography, thus allowing the duct to be closed, reducing the post-operative biliary discharge and infection.

Operative cholangiography is also preferable to post-operative, in that it may be repeated until the operator is satisfied that all stones are removed.

Following the findings in the post-operative cholangiogram in Figure 7, the duct was re-explored and a large stone removed. The patient died

post-operatively and at post mortem a further large stone was found. This had not been outlined because the dye had been held up by the stone above.

Operative cholangiography here, repeated until there was no further evidence of stones, would have prevented this error in interpretation. It has been claimed (Hicken *et al.*, 1954), that the error in interpretation of operative cholangiograms can be as low as 0.5 per cent., but even if this figure should prove a trifle optimistic, operative cholangiography is obviously a valuable adjunct to bile duct surgery.

THE PATHOGENESIS OF BILIARY CIRRHOSIS RESULTING FROM AN EXTRA-HEPATIC NON-MALIGNANT BILE DUCT OBSTRUCTION

What are the hazards of leaving stones in the ducts? Is it so important to free the ducts of stones other than by reason of the symptoms they cause? Can stones in the ducts cause trouble though they are giving little or no symptoms?

Effects of duct obstruction

It has long been recognised that the presence of stones in the bile ducts is dangerous by reason of two main complications—obstruction and infection.

Of these two factors there is no doubt as to which is the dominant in the mind of the clinician—obstruction. All jaundice due to an extra-hepatic cause has always been known as obstructive jaundice and the dramatic nature of the symptoms and signs of biliary obstruction has tended to focus attention upon it. For teaching purposes what have the malaise, rigors, slight fevers and leucocytosis of infection to offer in comparison with the pain, the jaundice with dark urine and clay coloured stools, the scratch marks and shiny nails of pruritus and the host of biochemical tests that are the natural sequelae of obstruction?

And yet, what are the actual dangers in the cessation of the flow of bile? The accumulation of bile pigments in the blood has never been shown to have any ill effect and the bradycardia thought to be associated with the retained bile salts is rarely of clinical significance. The xanthomata due to hypercholesterolaemia and the high serum level of alkaline phosphatase are no dangers to life. The only significant effect of the exclusion of bile constituents from the intestine, in all except the most prolonged obstructive jaundice, is the failure of absorption of Vitamin K, and the resulting hypoprothrombinaemia is readily corrected in the presence of adequate liver function.

The real danger to life lies in the effects of the duct stones on the liver. Here also the role of obstruction in the production of biliary cirrhosis has been emphasised by the more obvious and dramatic physical signs of bile retention. That bile duct obstruction can and does cause portal tract fibrosis cannot be denied. The early experiments of Rous and Larimore (1920) showed that experimental ligature of the common bile duct rapidly produced cirrhosis, a result, they thought, of the irritative nature of the retained bile. Yet the retained bile, found almost universally throughout the body in obstructive jaundice, in concentrations which may be far in excess of the normal, does not appear to result in the fibrosis of any viscera other than the liver. In the liver itself, the major bile retention is seen to be centrilobular, the fibrosis periportal.

Cameron (1932) has followed the changes in the portal tracts caused by common bile duct ligation and, while confirming that the formation of new fibrous tissue occurred, did not think that more fibrous tissue was formed than was necessary to support the proliferating bile ducts. The same authority (1958) has also noticed how the areas of necrosis caused by the microscopic rupture of the cholangioles are satisfactorily absorbed without fibrosis.

Effects of duct infection

While it must be admitted that obstruction can cause biliary cirrhosis, infection must be the more acceptable factor in the production of an organ scarred and infiltrated with inflammatory cells. No-one doubts the part played by infection in the scarred contracted kidney of chronic pyelonephritis. The induration and fibrosis of the pancreas induced by calculi is always referred to as chronic pancreatitis, and perhaps the part played by infection in the liver might have been more readily appreciated if the liver damage had been called chronic cholangio-hepatitis rather than biliary cirrhosis or chronic obstructive jaundice.

Sherlock (1958) claims that the term biliary cirrhosis should be applied to the pathological findings only and has given the name of chronic obstructive jaundice to the clinical picture. But what of the occasional cases of quite advanced chronic cholangio-hepatitis which can occur without any complaint of jaundice at any time? If jaundice occurs, as it usually does, it is not necessarily prolonged, as Figure 8 bears witness. Portal tract fibrosis is well established with marked bile duct proliferation, though jaundice had been present for only six days prior to the patient's admission, with no previous history other than vague abdominal symptoms and malaise for six months.

That obstruction is not essential has been shown by Cook *et al.* (1954), who described the development of biliary cirrhosis from widespread duct infection without any obstruction, calculous or otherwise. Symptoms of

recurrent bile duct infection are frequently mild and, unlike the alarming symptoms of jaundice, are often passed off as " gastric influenza " or some similar diagnosis and may be forgotten unless direct questions are put to the patient regarding them. The importance of these mild symptoms cannot be over-emphasized in the diagnosis of duct stones, for, though mild in themselves, they are clinical indications of serious potential liver damage.

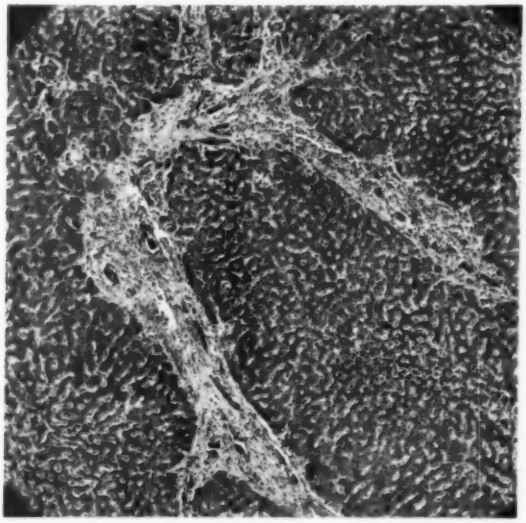


Fig. 8. Advanced degree of biliary cirrhosis seen in a patient with a history of jaundice of six days only. (Stained H. & E. × 50.)

The course of cholangio-hepatitis

Any patient with duct infection is always liable to a sudden acute exacerbation.

Figure 9 shows the liver of a patient who died from a fulminating cholangio-hepatitis and liver failure due to the stone at the lower end of the common duct. The infection has progressed to abscess formation in places, but even the less affected portal tracts, such as the one in Figure 10 (*a*), are widely infiltrated with inflammatory cells. Had the patient survived this infection, such portal tracts could hardly be expected to have healed without producing some degree of fibrosis.

While acute cholangio-hepatitis such as this is not the major factor in the production of permanent liver damage, it is not unusual to find cases where acute and chronic phases of the disease may be found side by side.

Figure 10 (*b*) is a liver biopsy taken from a patient with acute biliary tract infection. Adjacent to a necrotic cholangitic abscess can be seen a widened, fibrotic portal tract with infiltration by chronic inflammatory cells and with bile duct proliferation, all evidence of previous portal tract infection.

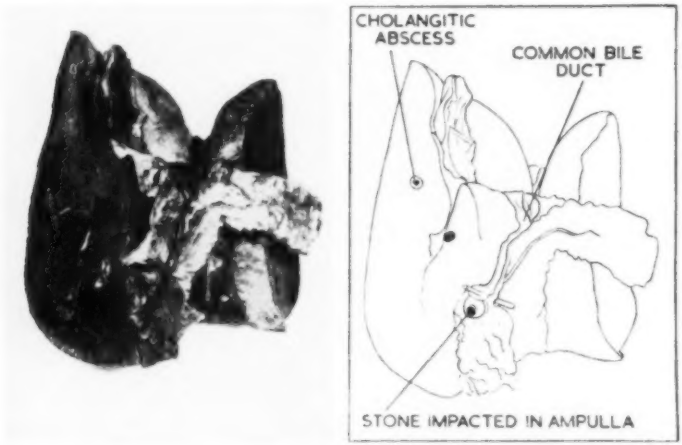
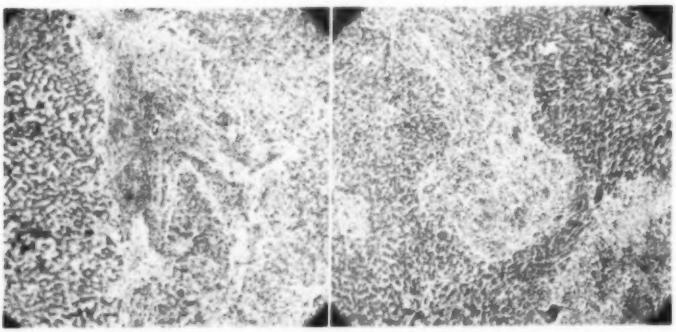


Fig. 9. Death from a fulminating cholangio-hepatitis due to a stone impacted in the Ampulla of Vater.



(*a*) (*b*)

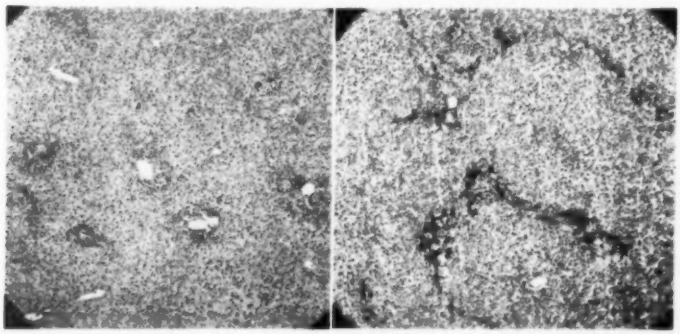
Fig. 10. (*a*) Widespread destruction of a portal tract by an acute cholangio-hepatitis. (Stained H. & E. × 35.)

(*b*) A liver biopsy showing coincident acute and chronic cholangio-hepatitis. (Stained H. & E. × 35.)

Just as the single severe acute infection is not the major factor in permanent liver damage, so there are mild degrees of duct infection that must be capable of complete resolution after the removal of the stone.

Figure 11 (*a*) is a liver biopsy taken from a patient at the time when stones were removed from his ducts. There had been no evidence, either clinical or operative, of any duct infection and it is readily imagined that the mild degree of subacute inflammation, seen around these portal tracts, is capable of resolution to normality after the removal of the stone.

A further stage in the progress of chronic cholangio-hepatitis may be seen in the liver biopsy in Figure 11 (*b*) taken from a patient with no symptoms or physical signs of duct infection but whose ducts were full of pus when the causative stones were removed. The distribution of the chronic inflammatory cells is just that which, if replaced by the fibrosis which is inevitable if the causative stones are not removed, would produce the pathological picture characteristic of biliary cirrhosis.



(*a*) (*b*)

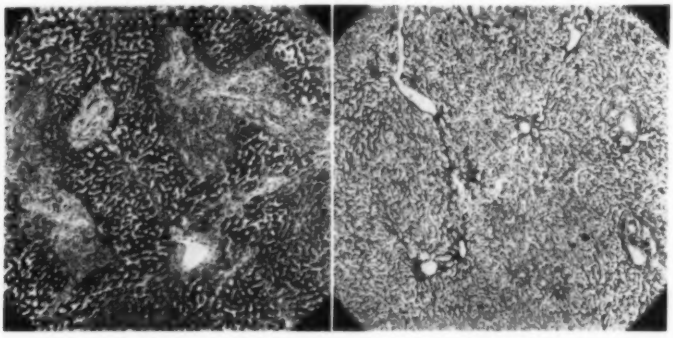
Fig. 11. (*a*) Calculous cholangio-hepatitis of this mild degree must obviously be capable of healing without permanent portal tract damage after the removal of the stone.

(*b*) The distribution of the cholangio-hepatitis in this liver biopsy is exactly that of the fibrous scarring of an established biliary cirrhosis.

The progressive nature of biliary cirrhosis

It is obviously difficult to study the early progressive stages of the disease in clinical practice—most of the cases are already well advanced on diagnosis. Thus the following case is of interest because the actual time of onset of the bile duct damage and infection is accurately known, though it must be remembered how difficult it is to relate the maturity of the portal tract changes to the duration of duct infection when the degree of underlying obstruction is notoriously variable.

The common bile duct was damaged in a man aged 33 years during partial gastrectomy for duodenal ulcer. Symptoms of duct infection were immediate with jaundice, rigors, a pyrexia of 103 degrees, exquisite tenderness over the liver and leucocytosis. These symptoms were re-

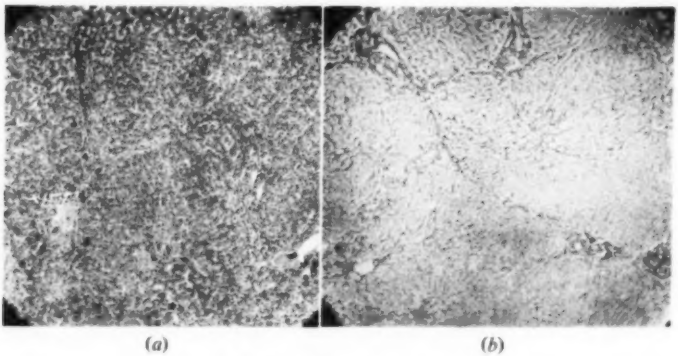


(*a*) (*b*)

Fig. 12. A liver biopsy after three months of duct infection.
(*a*) Stained with H. & E. × 35 to show the acute cholangio-hepatitis.
(*b*) Reticulin stained × 35 showing no portal tract fibrosis.

current and severe over the next three years, operations on the biliary system being performed on five occasions, liver biopsies being taken at three of these operations.

The first biopsy (Fig. 12 (*a*)) was taken after three months of duct infection. This shows all the features of acute inflammation short of

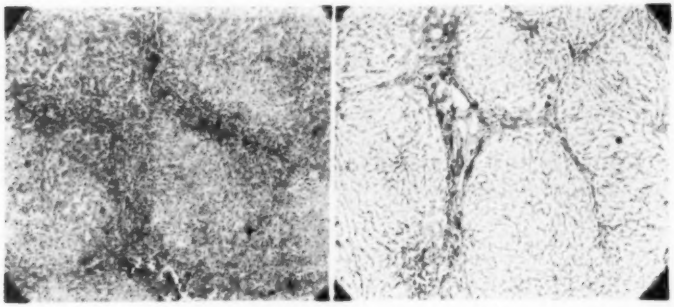


(*a*) (*b*)

Fig. 13. (*a*) The liver biopsy after nineteen months' duct infection. (Stained H. & E. × 35.)
(*b*) Reticulin stained × 35 to show the early fibrosis linking portal tracts.

suppuration. Bile duct proliferation has already commenced though there is, as yet, no fibrosis.

The next biopsy (Fig. 13 (*a*)) was taken after nineteen months and shows the acute phase to have subsided and is replaced by a more subacute reaction. Fibrosis, though generally slight, is beginning to appear. This fibrosis is beginning also to delineate the lobular pattern.



(*a*) (*b*)

Fig. 14. (*a*) The liver biopsy after thirty-five months of duct infection. (Stained H. & E. × 35.)

(*b*) Reticulin staining shows the well established biliary cirrhosis.

In the final biopsy (Fig. 14 (*a*)), taken after thirty-five months, this outlining of the lobular pattern is seen to be well established.

The progressive scarring of the portal tracts produced by this duct infection is better appreciated in slides of the same liver biopsies treated with a reticulin stain.

It can be seen in Figure 12 (*b*) that there is no portal tract fibrosis after three months. After nineteen months (Fig. 13 (*b*)), however, and again in the final biopsy after thirty-five months (Fig. 14 (*b*)), the scarring is appreciable, the cirrhotic process linking one portal tract to its neighbours by strands of fibrous tissue outlining the liver lobules.

These progressive pathological findings in the liver are developing in a patient whose clinical picture is predominantly that of a severe infection. The portal tracts are now virtually converted to chronic granulomatous inflammatory lesions, with fibrosis and inflammatory cells around damaged and proliferative bile ducts and even restoration of normal duct function at this stage will scarcely eradicate the infection from the grossly distorted and scarred portal tracts.

Persistence of symptoms following the removal of duct stones may occasionally be due to an intrahepatic obstructive cholangio-hepatitis, as

seen in a case to be presented later (Figs. 19 and 20), and it is more readily imagined that the results of duct infection should persist and progress than the results of obstruction. Stewart and Lieber (1934) have in fact been impressed by the reparative powers of the liver following the relief of duct obstruction.

"EXTRA-HEPATIC" BILIARY CIRRHOSIS AND PORTAL HYPERTENSION

This progressive characteristic of chronic cholangio-hepatitis, together with the irreversible nature of its later stages, is worthy of note in view of one of the less common complications of duct stones, portal hypertension. It has not always been recognised that portal hypertension could result from biliary cirrhosis, Whipple (1954), in an early description of the condition, stating that Banti's syndrome was not characteristic of the biliary and cardiac cirrhoses.

MacPhee (1956) has more recently described how portal hypertension is characteristic of the later stages of primary intrahepatic biliary cirrhosis, but severe bleeding from oesophageal varices is still rather unusual to associate with non-malignant condition of the extrahepatic biliary duct system.

Portal hypertension due to bile duct stricture

A female patient aged 53 years had undergone cholecystectomy twenty years previously and, following repeated attacks of pain and jaundice, an exploration of her bile ducts seventeen years later. On examination the patient was dark skinned, but was not jaundiced. Spider naevi and liver palms were noted and, though the liver was palpable one inch below the costal margin, the spleen could not be palpated. Her serum bilirubin was only 0.5 mgms. per cent., but her liver function tests showed evidence of considerable cellular damage. A barium swallow was seen to show extensive oesophageal varices.

Three months later the patient had a severe attack of malaise, rigors and jaundice. At laparotomy, extensive collateral venous blood flow was encountered and the liver was found to be very hard with a fine irregular surface. A dilated common hepatic duct was opened, two stones removed and choledochoduodenostomy performed.

The post-operative cholangiogram in Figure 15 shows the extent of the stricture responsible for the cirrhosis and portal hypertension.

The importance of the association of bile duct stricture and portal hypertension has been emphasised by Cole *et al.* (1955) reporting the incidence of portal hypertension in 29 of his 122 cases of bile duct stricture, four

of the patients actually succumbing to this complication of the disease. But it is not essential to have the degree of obstruction and resulting infection due to a duct stricture to produce portal hypertension—the complication *can* arise from calculous disease of the ducts.

Portal hypertension due to bile duct calculi

A liver which showed the finely irregular surface and tawny colour, typical of biliary cirrhosis, was found at post mortem examination of a female patient aged 69 years, who had been jaundiced for a few days only prior to admission though vague epigastric pain had been present for some years.

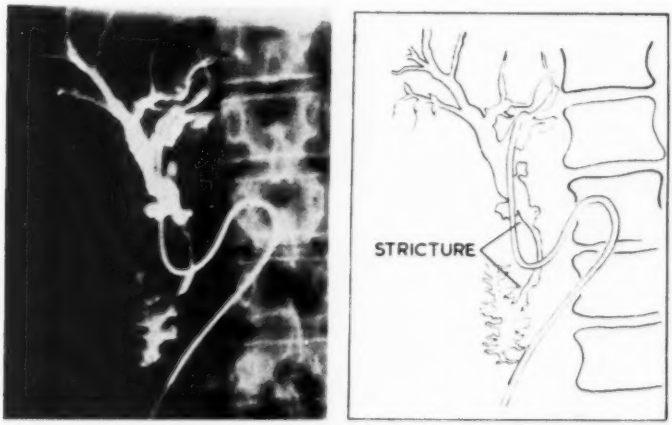


Fig. 15. An extensive stricture of the common bile duct which resulted in the patient developing portal hypertension.

On examination she was deeply jaundiced, her serum bilirubin being 16 mgms. per cent. Her liver function tests showed evidence of considerable liver damage, while a white cell count of 14,600 per c.mm. suggested duct infection.

At operation, there was bile-stained ascites with obvious collateral venous engorgement. The common bile duct was grossly dilated, containing two large mixed stones which were removed and a choledochostomy performed.

A liver biopsy showed all the features of chronic cholangio-hepatitis together with superadded acute inflammation.

The patient died in hepatic coma five days post-operatively and, at post mortem, varices were present in the lower half of the oesophagus.

The spleen, which weighed 150 G., showed, on microscopic examination, the fine pulp fibrosis and sinus dilatation typical of portal hypertension, though the absence of periarterial haemorrhages and siderotic nodules is to be noted (Fig. 16).

Though a history of obstructive jaundice was present for a few days only in this case, there was no history of jaundice at all in the case of an old lady aged 85 years who was admitted because of a sudden severe haematemesis from which the patient died.

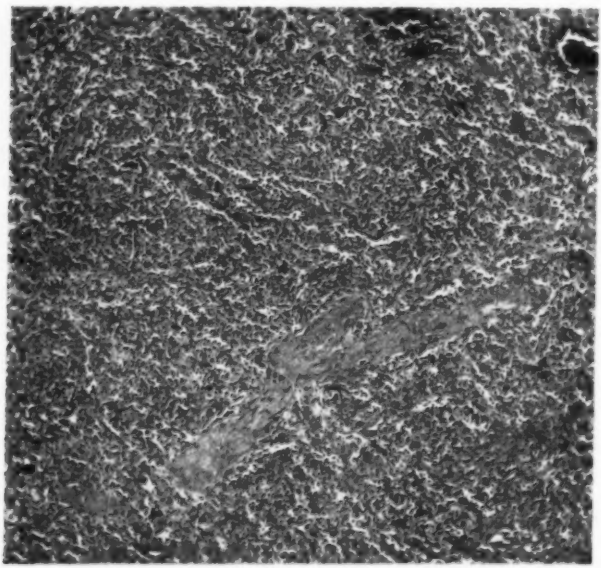


Fig. 16. The splenic pulp fibrosis and sinus dilatation, typical of portal hypertension, are due here to biliary cirrhosis. There is an absence of periarterial haemorrhages or fibrosis. (Stained H. & E. × 50.)

Enquiries from her general practitioner confirmed that there had been no history of jaundice, but that one year previously, on a diagnosis of a Kelly-Paterson syndrome, a barium swallow was performed.

Though the upper oesophagus revealed the usual post-cricoid web, the normal appearance of the lower half of the oesophagus is shown in Figure 17. At post mortem examination twelve months after these X-rays, there were extensive oesophageal varices up to the level of the aortic arch. The gall bladder was shrunken and fibrotic. The biliary duct system was

grossly dilated. The ducts contained much turbid biliary mud and one mixed gall stone which, at post mortem, was lying in the common hepatic duct.

The macroscopic appearance of the liver was typical of biliary cirrhosis. The histological appearances in Figure 18 are also typical of chronic cholangio-hepatitis with widened scarred portal tracts containing mononuclear cells and proliferating bile ducts.

The spleen, which weighed only 145 grammes, showed the microscopic appearances of fine fibrosis throughout the splenic pulp with some broadening of the larger trabeculae but again with no periarterial haemorrhages.

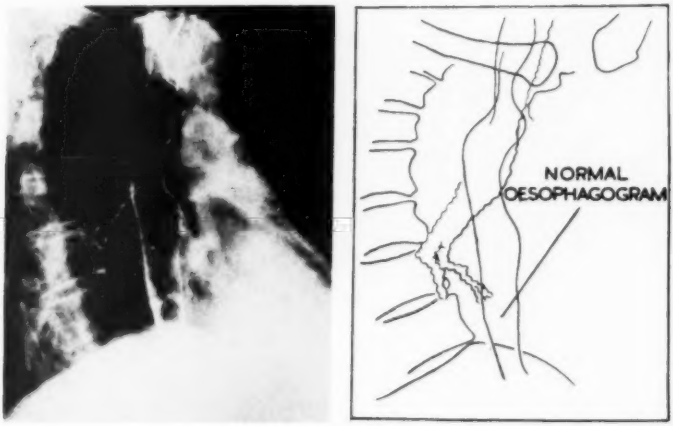


Fig. 17. A normal oesophagogram performed twelve months before a fatal haematemesis from oesophageal varices caused by the calculous biliary cirrhosis seen in Fig. 18.

Features of portal hypertension due to biliary cirrhosis

The portal hypertension in these three cases is plainly caused by chronic cholangio-hepatitis, secondary to a duct stricture in one and to calculous disease in the others. It is not surprising that chronic cholangio-hepatitis should give rise to portal hypertension for the perivenous fibrosis, the portal tract vascular abnormalities and the pressure from regenerating nodules, thought to cause the venous block in portal cirrhosis, are present in this disease also. There are, however, differences demonstrated by the previous cases, which should modify their clinical management.

Though it has been shown that severe chronic cholangio-hepatitis may develop without clinical jaundice, many of the cases presenting for surgery

will have clinical or subclinical jaundice with the correspondingly increased hazard of bleeding from oesophageal varices, or at operation complicated by extensive collateral veins.

It must also be remembered that there are two aims in treatment—the establishment of an increased collateral circulation and the removal of the causative biliary tract disease. Which should be undertaken first? Cole *et al.* (1955) has suggested that a preliminary shunt operation tends to facilitate the procedure on the bile ducts, but it is felt that no time should be lost in removing the underlying cause of the progressive liver disease especially if jaundice is present. This is particularly so in the case of duct stones, for the dangers of haemorrhage from collateral vessels when exploring the

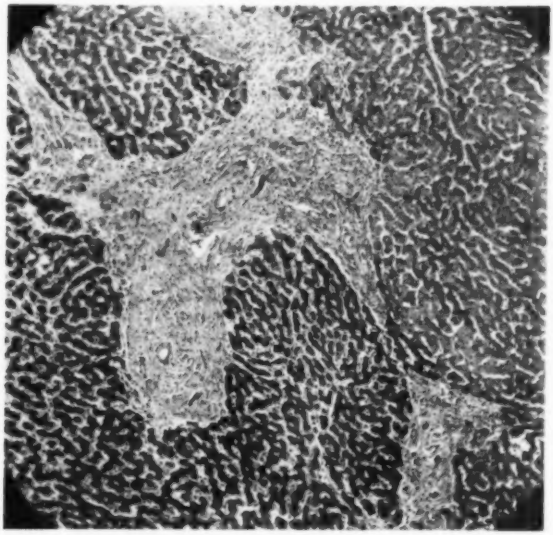


Fig. 18. The patient with this severe degree of biliary cirrhosis gave no history of jaundice, her first symptom referable to the cirrhosis being a fatal haematemesis. (Stained H. & E. × 50.)

duct for stones is far less than when attempting to relieve a stricture, with its inevitable very vascular periductal adhesions. This has been noted by Hunt (1958), who also advises against a simultaneous attack upon both the vascular and the biliary obstructions.

The progressive nature of chronic cholangio-hepatitis and the irreversible nature of its later stages has been stressed earlier and assumes greater significance in its relationship to portal hypertension.

Though a great deal has still to be learnt as regards the exact aetiology of portal cirrhosis, it is agreed by many authorities (Walker, 1954; Sherlock, 1958) that, once the reparative processes are complete, it is relatively a static condition in most cases. That is to say that, provided the patient has a well developed collateral venous circulation and does not sustain a mortal oesophageal haemorrhage, there is no reason why liver failure should not be averted for a considerable time. In chronic cholangio-hepatitis, however, the cause of the hepatic fibrosis is still present, of long standing and in many cases, such as duct strictures, difficult to eradicate, giving the liver damage its essentially progressive nature.

With the slowly progressive liver picture in mind, it would be natural to think of the onset of portal vein obstruction as being equally slow. The degree of cholangio-hepatitis seen in the last case, however, does not develop within a few months and yet there were no oesophageal varices present twelve months prior to her fatal haemorrhage, as demonstrated by the barium swallow performed for an unrelated condition. It would appear, that, though the liver damage may be slowly progressive, the onset of portal vein obstruction, at least as detectable by barium studies, may be relatively sudden.

As regards the microscopic appearances of the spleens in the three cases of portal hypertension due to gall stones presented here, though the pulp fibrosis and sinus dilatation typical of portal hypertension are present, there is no evidence of periarterial haemorrhages or siderotic nodules. This may well be a coincidence considering the small number of cases involved; but one wonders whether the periarterial haemorrhages and resultant fibrosis would be more likely to occur as a result of relatively sudden portal obstruction, due to a portal vein thrombosis or even the scarring following a severe virus hepatitis and whether the absence of siderotic nodules in these spleens is but another reflection of the gradual but remorseless progress of the calculous cholangio-hepatitis.

SUMMARY

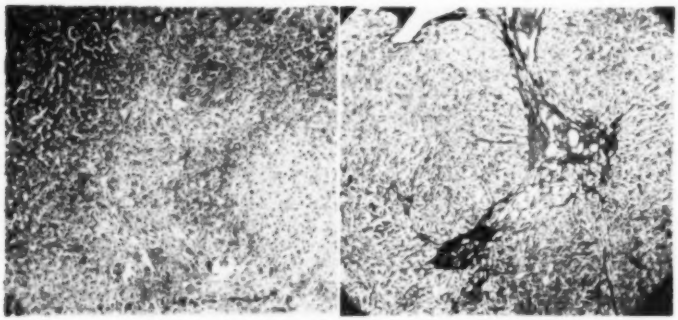
Finally, to summarize, I would like to present this last case which demonstrates many of the features of the disease which I consider are of importance.

A woman aged 49 years was operated on because of biliary colic and obstructive jaundice which had been present for six weeks. A large stone, impacted in the Ampulla of Vater, was removed from a grossly dilated bile duct and a functionless fibrosed gall bladder excised. The history of biliary colic and the operative finding of a grossly dilated common bile duct are stressed as evidence that this is not a case of a primary intra-hepatic cirrhosis with coincidental duct stones.

Following this operation there was no relief from her jaundice, her serum bilirubin remaining at 19 mgms. per cent. and a second exploration of her duct was performed six weeks later. A post-operative cholangiogram confirmed the operative findings that there was now no obstruction in the bile ducts to account for the continued jaundice.

A liver biopsy taken at that operation (Fig. 19 (*a*)) shows only moderate portal tract fibrosis with some superadded acute inflammation.

Though these liver changes are only slight, they are obviously (1) not to be reversed by the removal of the stone and (2) are sufficient to constitute an intrahepatic block in replacement of the previous extrahepatic obstruction due to the stone.



(*a*) (*b*)

Fig. 19. (*a*) A liver biopsy showing biliary cirrhosis which has caused continued jaundice after removal of duct stones. (Stained H. & E. · 35.)
(*b*) The extent of the portal tract fibrosis shown with a reticulin stain · 35.

The T-tube was left *in situ* for three months, but no bile ever drained through it and the patient was still jaundiced six months post-operatively. The patient failed to attend further until she reappeared fifteen months later with melaena, haematemeses and ascites. Her serum bilirubin was now only 0.9 mgm. per cent., but her white cell count was 15,000 per c.mm. and both the liver and spleen were readily palpable.

In view of her severe haemorrhage and the two previous explorations of her porta hepatis, a lieno-renal anastomosis was considered but, the splenic vein proving unsuitable, a splenectomy and gastric transection was performed, the spleen weighing 170 G.

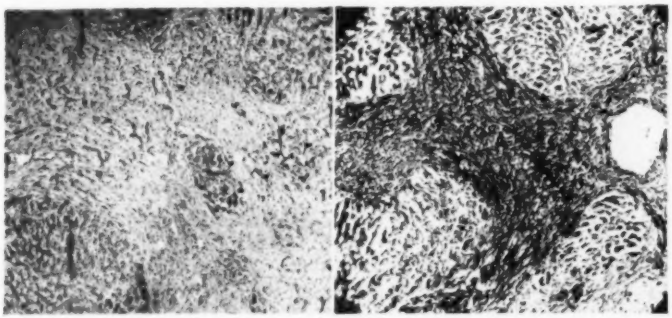
The histological appearances of the spleen showed pulp fibrosis and sinus dilatation but again the absence of siderotic nodules was a feature, perhaps as a result of the portal block being gradually built up over the previous two years.

The patient remained fairly well without further haemorrhage but requiring repeated paracenteses abdominis, until suddenly, a further two years later, she was admitted in hepatic coma and died.

At post mortem examination, all the evidence of portal hypertension was present and the absence of residual bile duct obstruction confirmed.

The extent of the liver fibrosis, however, is of considerable interest in that it demonstrates the progressive nature of the disease (Fig. 20 (*a*)).

This is fibrosis, instigated by the duct stone and perpetuated after the stone's removal by the portal tract infection.



(*a*) (*b*)

Fig. 20. The microscopic appearance of the same liver as in Fig. 19, but four years later, showing how the biliary cirrhosis has progressed to an extreme degree even after the complete removal of duct stones.

(*a*) Stained with H. & E. × 35.

(*b*) Reticulin stained × 35.

This is perhaps better appreciated with slides stained to show the fibrous tissue. Compare the original liver biopsy seen in Figure 19 (*b*), with the liver at post mortem four years later seen in Figure 20 (*b*). It is obvious that, in a certain number of cases, removal of a stone in the earliest stages of cholangio-hepatitis will not stay its progress to the advanced stage seen here, or prevent the onset of portal hypertension.

ACKNOWLEDGMENTS

My grateful thanks are due to Professor Lambert Rogers for his constant encouragement and advice and also to the surgeons of the United Cardiff Hospitals for their permission to use the clinical material. I am indebted to Mr. Ralph Marshall for the clinical photography and to Miss Pat Henshall for the secretarial work.

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CYSTS OF THE KIDNEY

Lecture delivered at the Royal College of Surgeons of England

on

29th April 1959

by

J. D. Fergusson, M.A., M.D., F.R.C.S.

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ALTHOUGH CYSTS OF different kinds may arise in many structures throughout the body there is probably no organ in which a greater variety occurs than the kidney. The complex development and final highly differentiated structure of this organ, coupled with its liability to all types of morbidity, seem to render it particularly susceptible to lesions of this nature. While the type of cyst and the extent to which the kidney is involved may vary considerably according to the cause, there are numerous intermediate states in which the aetiology remains in doubt and precise classification is thus rendered difficult. Taking the more characteristic examples of cystic disease, however, it is possible to draw up a provisional scheme of nomenclature as shown in Table I.

A mere glance at this table is sufficient to indicate that the various categories differ greatly both in incidence and clinical importance.

Renal dysplasia is an uncommon condition in which the pelvis and calyces fail to develop and small cysts may develop in the shrunken metanephrogenic cap. These by themselves are clinically insignificant and for practical purposes need only be regarded as incidental to the underlying embryological defect.

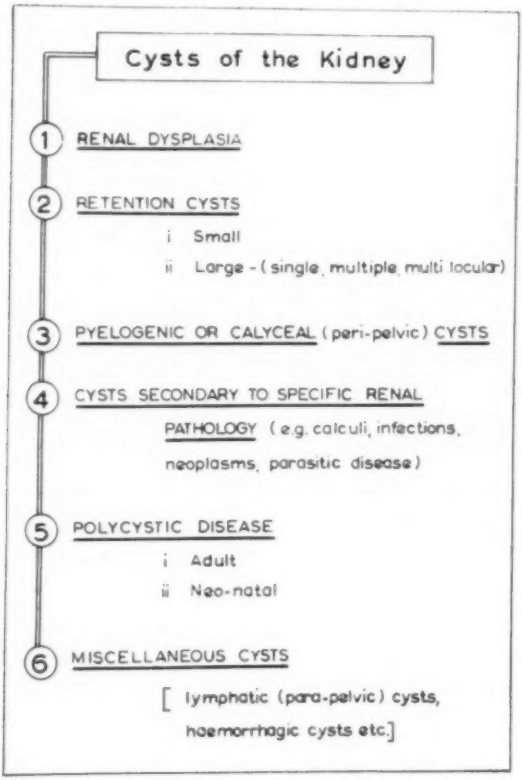
Small retention and inflammatory cysts, although frequently observed in the post-mortem room, likewise have little or no importance during life and generally escape recognition save as a casual finding during surgical procedures. Cysts of this nature are stated often to occur in association with the scarred kidney of nephritis, but there are many instances where evidence of previous inflammation is lacking and the kidney otherwise appears essentially normal. It may thus be difficult to draw a distinction (except on grounds of size) between these and the larger simple parenchymatous cysts which, although often multiple, are sometimes better known by the title " solitary " renal cysts.

These larger cysts may assume considerable dimensions and achieve both clinical and radiological significance during life. Presenting usually as rounded masses related to the kidney their importance lies mainly in

the realm of differential diagnosis and in their occasional liability to complications. These matters will be referred to in greater detail later.

Pyelogenic or calyceal cysts of true developmental origin are undoubtedly rare and most recorded cases are probably instances of secondary cavitation due to some specific underlying renal pathology. A single

TABLE I



example of the latter may here suffice (Fig. 1) showing solitary cystic expansion of a minor calyx containing stones in the central portion of the right kidney. Treatment consisted of wedge resection of the portion of the kidney including the cavity, and a normal pyelogram (minus the affected calyx) was subsequently obtained. Histological examination failed to differentiate between a primary calyceal cyst and secondary hydrocalicosis associated with stone formation.

Other cysts associated with specific renal lesions include those occasionally found in relation to local inflammatory conditions and tumours; and also the true parasitic cysts.

Whereas most of the cysts so far described only encroach on the renal

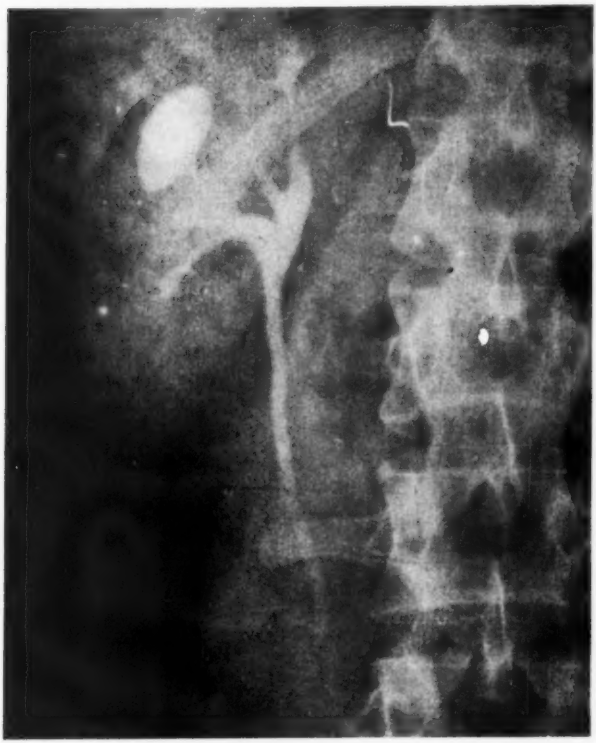


Fig. 1. Pyelogram showing cavity relating to a minor calyx of the right kidney. Probably an example of hydrocalicosis rather than a primary calyceal cyst.

substance to a limited extent there is another group in which the process is more diffuse and in which characteristically most of the kidney becomes affected. Diffuse cystic involvement or " polycystic disease " of the kidney may be divided into two forms according to whether it presents at birth (or in early childhood) or during adult life. The latter type exhibits certain structural and genetic features which fully establish it as a distinct entity, whereas the neo-natal condition is far less clearly defined and may

well, in fact, be unrelated. As the adult form of the disease is of considerable clinical and therapeutic interest it will be referred to in greater detail subsequently.

Finally, there is an assortment of miscellaneous conditions which are not entirely unique to the kidney and which include lymphatic (or so-called " parapelvic ") cysts, haemangiomatous expansions and occasionally true haemorrhagic cysts resulting from trauma. These are all comparatively uncommon and often unobtrusive, but sometimes give rise to difficulty in diagnosis on account of their clinical and radiological features.

From the foregoing brief review it becomes clear that, apart from specific secondary lesions which are dealt with on the merits of their underlying pathology, there are two types of cystic disease which, on account of their clinical incidence and importance, warrant more detailed study. These are polycystic disease and simple parenchymatous (or solitary) cysts.

POLYCYSTIC DISEASE OF THE KIDNEY

Polycystic disease of the kidney has been described as a disease of paradox, manifesting itself typically in the new born and middle-aged and lying concealed in childhood. The two peaks of incidence are clearly shown in Küster's study of 239 cases at the beginning of the present century (Fig. 2). At one extreme of age there is a number of cases in which the condition is so advanced at birth as to prejudice survival, while the remainder appear compatible with normal existence until adult life, when they gradually first advance to clinical prominence. This peculiar distribution and behaviour, which appears unusual in a disease generally held to be of congenital origin, immediately renders it doubtful whether the two groups are in fact aetiologically related. As will be seen presently there are strong grounds for regarding them as distinct, but for the moment only the adult form will be considered on account of its major clinical interest.

By definition, polycystic disease implies a widespread cystic replacement of the renal parenchyma and one cannot do better than quote a recent description by Dalgaard (1957): " A polycystic kidney is one in which the tissue is displaced by a large number of tightly packed cysts so that the cystic volume predominates over the solid part to a considerable degree." This definition alone will generally serve to exclude examples of multiple simple cystic disease. Usually, though not invariably, a considerable increase in volume of the kidney takes place, and the surface of the organ becomes studded with numerous cysts giving rise to an appearance compared as long ago as 1763 by Littre to a " bunch of grapes ". Large polycystic kidneys may reach an enormous size and weights of up to 15 lbs. have been recorded.

The " full blown " adult condition is typically bilateral and, although a few cases of multiple cysts in a single kidney have been reported by Moore (1957), many authorities emphatically deny the existence of unilateral disease. It is well known, however, that the intensity of the process may differ on the two sides and that " clinically " one kidney may be obvious

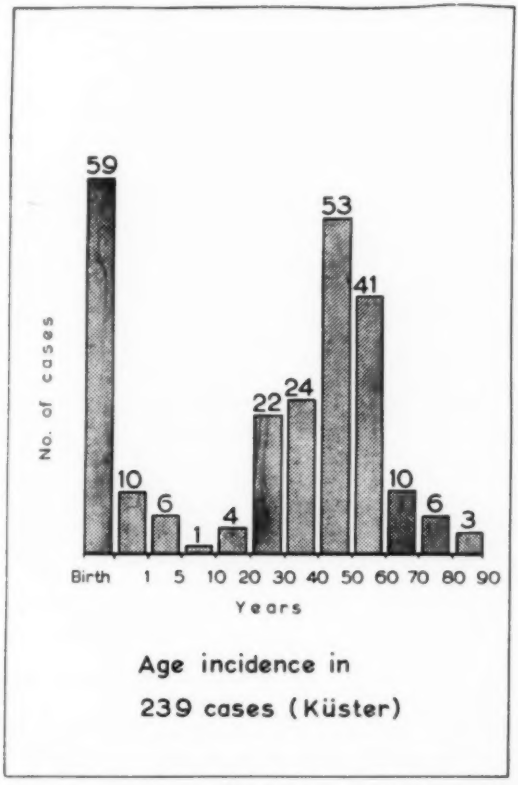


Fig. 2. Polycystic disease of the kidney showing age incidence (Küster, 1902).

while the other remains impalpable. Many records of unilateral disease are undoubtedly based on single surgical specimens of this type where the disease on the opposite side has not progressed sufficiently to indicate its presence. A personal case, in which a polycystic kidney had been removed elsewhere some years before, was brought to light by rupture of the remaining kidney during a bombing incident. After recovery with conservative treatment the residual kidney was confirmed both clinically

and radiologically as polycystic. A report from the previous records, however, showed that this kidney had been regarded as normal at the time of operation.

Another source of error may arise from the misinterpretation of single kidneys affected by multiple simple cysts as examples of polycystic disease (Fig. 3). The resemblance sometimes indeed may be so close as to

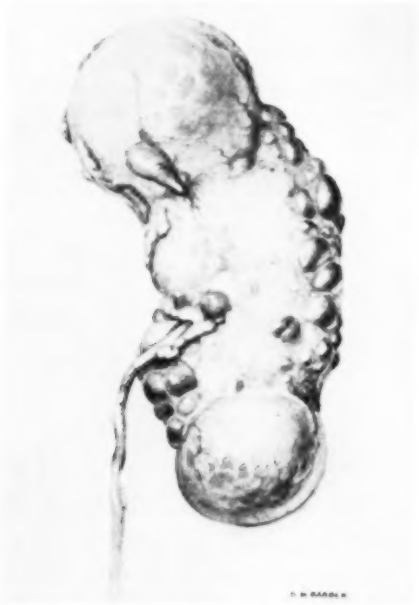


Fig. 3. Multiple " simple " cysts of the kidney simulating polycystic disease.

suggest a common aetiological factor. Herbut (1952) in fact has given his opinion that most, if not all, simple cysts are of congenital origin and explicable on the same basis as the polycystic condition. Nevertheless there are certain arguments against this view and multiple simple cystic disease may generally be distinguished by its limited involvement of the parenchyma and by the fact that some of the cysts at least are disproportionately large and grossly distort the renal outline.

For practical purposes, therefore, the true adult polycystic condition should be regarded as a distinct entity in which the disease is essentially widespread and bilateral. This conception may be of considerable importance in planning its appropriate management.

It is not the purpose of this review to give a comprehensive description of the disease, but rather to direct attention to some of its more interesting and problematical facets. These include its incidence and familial tendency, certain diagnostic and prognostic implications arising therefrom and, finally, various matters relating to its treatment.

Incidence

It is abundantly clear from post-mortem statistics that polycystic disease may sometimes escape clinical recognition and may indeed even prove compatible with a normal span of survival. While autopsy records suggest an average incidence of 1 in 400 post-mortems the clinical frequency among hospital patients amounts to nearer 1 in 4,000 (Fergusson, 1949). Although, as emphasized by Dalgaard (1957), the two groups are not directly comparable, there can be little doubt that the latent disease is more common than is generally supposed. Nevertheless, while the undetected disease may carry a comparatively good prognosis, cases which are diagnosed clinically usually progress towards a fatal outcome within a few years of their recognition.

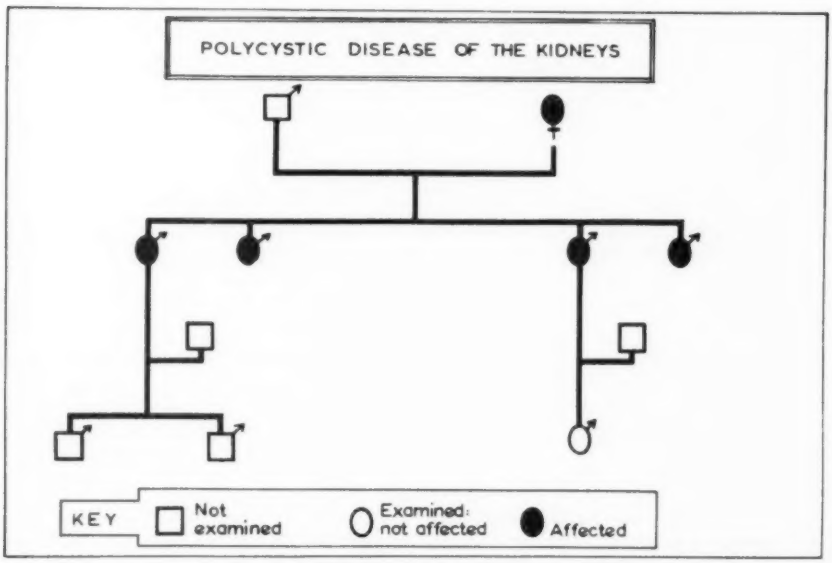


Fig. 4. Genetic table showing 4 male members of the first generation affected by polycystic renal disease and presenting with hypertension. No urinary symptoms were in evidence.

Diagnosis

The diagnosis of the disease may be suggested by the symptomatology and clinical findings supplemented by pyelographic evidence. A history of familial affection provides the strongest confirmation. It is of interest to note that despite widespread renal involvement, urinary symptoms may sometimes remain in abeyance. Among personal records of familial cases there were four brothers (between the ages of 40 and 50) all of whom were oblivious of the presence of enormous renal masses (Fig. 4). The eldest brother died from a hypertensive cerebro-vascular accident and at post-mortem was found to have large polycystic kidneys weighing just over 7 lb. each. Two years later the next brother died from subarachnoid

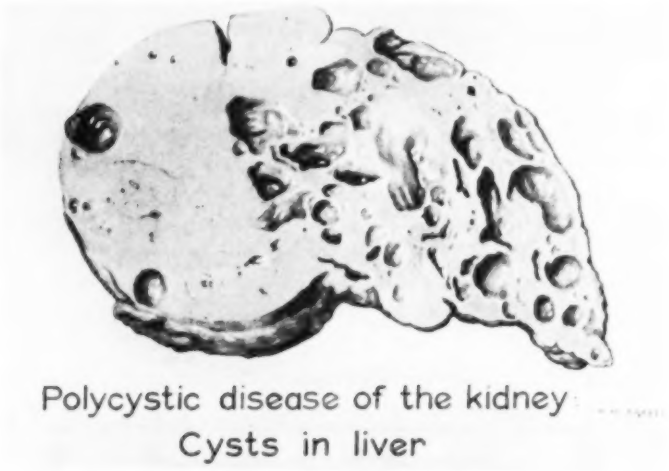


Fig. 5. Section of the liver from a case with polycystic renal disease showing multiple macroscopic cysts.

haemorrhage and a year later the third brother followed suit. The fourth remains alive, but is severely hypertensive. None of these patients ever evinced any urinary disturbance and, indeed, symptoms were conspicuously absent save for the penultimate evidence of rising blood pressure.

Such cases are, however, perhaps unusual and most patients either complain of renal pain or present with recurrent bouts of haematuria or urinary infection with gradual progression to renal failure and ultimate death from uraemia. Nevertheless the liability to hypertension and intra-cranial haemorrhage should always be borne in mind, particularly if it is proposed to attempt any form of surgical treatment.

Recent investigations strongly support an occasional association between polycystic disease and the presence of congenital aneurysms of the basal arteries of the brain—the coincidence occurring with sufficient frequency to suggest a genetically determined syndrome. It should be emphasized that such aneurysms do not constitute true cysts and, despite certain statements in the textbooks, there is no evidence to support the view that the cerebellum is involved in the polycystic process. Other organs, however, may be affected by cyst formation, notably the liver (Fig. 5), although, apart from this organ, the coincidence appears too small to be of statistical significance. Macroscopical cystic involvement of the liver may be observed in upwards of 15 per cent. of cases and enlargement of this organ sometimes confuses the diagnosis.

Familial tendency

Some indication has already been given of the familial tendency of the disease and indeed this has for long been recognized. While apparently isolated cases are often encountered in clinical practice the lack of opportunity for detailed family investigation may often account for this. The earliest suggestion that the disease might be inherited is probably attributable to Adamkiewicz in 1843, following which numerous examples of familial affection have been described, including the well known report by Cairns in 1925. Some ten years ago I presented a brief review of the hereditary pattern of the disease based on a personal experience of six families augmented by a further study of 84 family records from the literature embracing 307 cases in all (Fergusson, 1949). Since then, an exhaustive report on 284 Danish patients and their families has been made by Dalgaard (1957), and it is upon this combined experience that the following observations are based.

The large number of familial examples of polycystic disease, in some instances extending over four generations (Fuller, 1929) leaves little doubt as to the hereditary nature of the process. Such records show that males and females are affected in similar proportion and that the disease may be transmitted with equal frequency by either parent. In the personal series analysed ten years ago the sex distribution (where stated) amounted to 132 males and 115 females and the affected parent was male in 35 instances and female in 33. In Dalgaard's material female cases slightly predominated (193 females—157 males), the average age on diagnosis being 47 years (between the extremes of 16 and 85).

It is unusual, even in the presence of an impressive family history, for the adult form of the disease to be recognized in childhood. The youngest case in my own material was a boy of five who had previously had a right renal exploration for suspected tumour and was unexpectedly found to have a polycystic kidney (Fig. 6). Subsequently his father was investigated for urinary infection and found to have bilateral polycystic kidneys, while a

year or two later an uncle died from pneumonia and was found at autopsy to have a similar renal condition. In most cases, however, the disease does not become apparent until middle age and then follows a similar pattern in all affected members of the same family. Attention has previously been drawn to the hypertensive disasters which befell three out of four brothers at a similar age and the complete absence of urinary symptoms in this particular family. In another family five out of twelve members of a generation were affected (Fig. 7) and all in turn presented with symptoms of recurrent urinary infection and haematuria between the ages of 37 and 40. None survived beyond the age of 45.

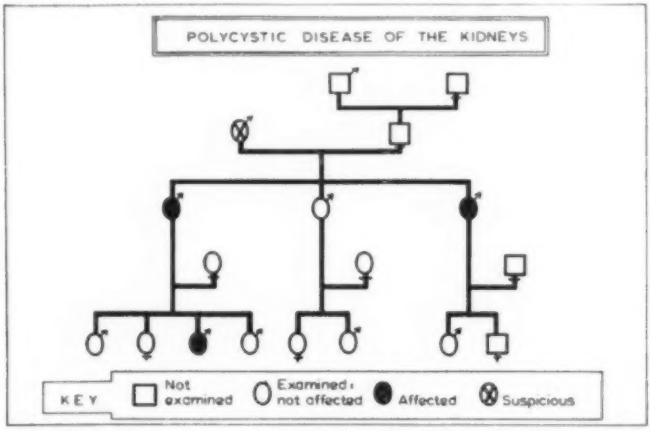


Fig. 6. Genetic table illustrating distribution of polycystic disease in a family in which a boy of 5 showed clinical evidence of the adult form of the disease. The boy's father and uncle were similarly affected.

It seems, therefore, from these and other examples that not only may the symptomatology often run parallel in certain families, but also the prognosis. This may, of course, be partly due to environmental factors in addition to the underlying genetic disturbance. There seems little evidence, however, to support the suggestion advanced by Cairns that younger affected siblings die at an earlier age than their seniors.

Since all the genetic evidence at present available suggests that the adult polycystic condition is inherited as a dominant characteristic on Mendelian lines it is natural that some anxiety should be felt by affected parents as to whether their children are likely to develop the disease. Pyelographic records during childhood generally fail to show the dormant process and among over 20 children of affected parents personally investigated in this manner only one case (a girl of 15) was regarded as suspicious. Likewise

attempts to reveal the disease by association with other inherited factors have also been unavailing. During my study of the familial condition a large number of investigations were carried out in the hope of detecting a linkage with some easily recognizable genetic factor. These included a detailed analysis of the blood groups and various genetically determined physical characteristics in both affected and unaffected members of the families concerned (Figs. 8 and 9). No linkage, however, could be confirmed with any established hereditary trait so that the results of the experiment could only assume a negative importance. From the genetic standpoint, therefore, all that can be said at present is that the position

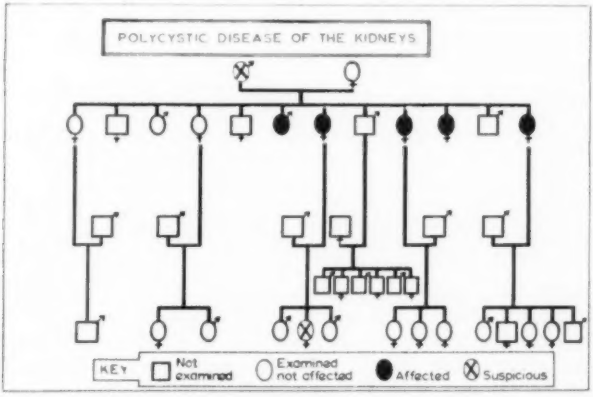


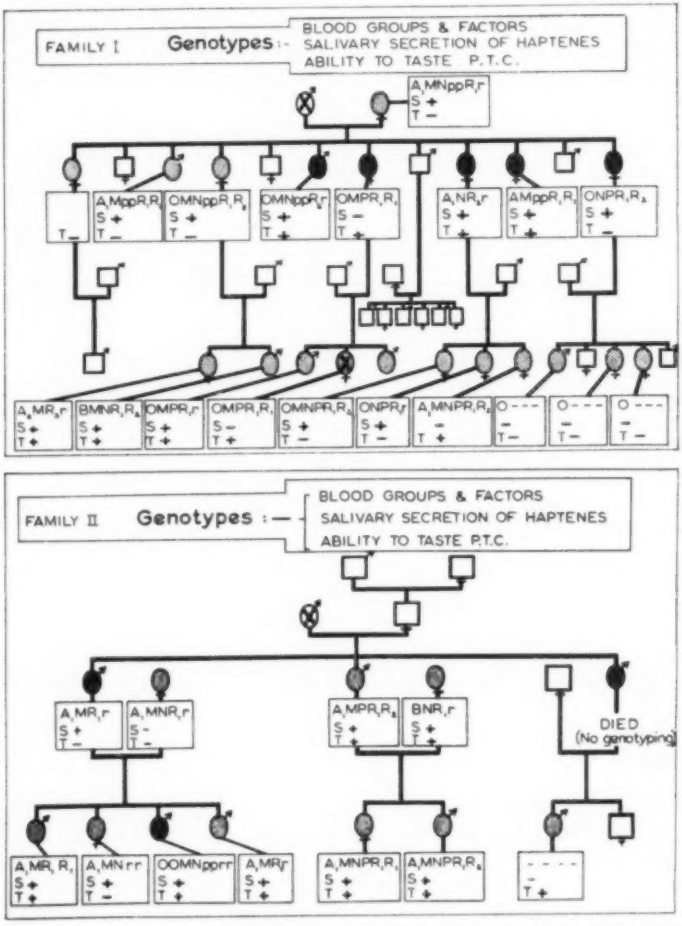
Fig. 7. Genetic table showing 5 cases of polycystic renal disease in a single generation of 12 members. All the affected individuals presented with similar symptoms and all died before the age of 45.

of the gene determining polycystic development remains unknown, but owing to the almost equal incidence of the disease in males and females it is unlikely to be associated with the sex chromosome.

Treatment

With regard to treatment of the fully established disease in adult life controversy continues mainly on the merits or otherwise of various surgical procedures. Remembering the strong bilateral tendency of the condition and the consequent dearth of functional renal tissue it can seldom be justifiable to remove a polycystic kidney save for the most compelling reasons. Instances of severe rupture with continuing profuse haemorrhage and cases complicated by malignancy or serious infection may fall within this category. For the remainder the choice lies between appropriate conservative treatment on medical lines and the application of

palliative surgical procedures designed to relieve pain or to encourage renal function. The latter may comprise simple aspiration of the cysts, decortication of the kidney or marsupialization with repeated puncture at intervals. It remains exceedingly doubtful whether, in fact, renal efficiency is ever improved by such measures and, indeed, Bricker and Patton



Figs. 8 and 9. Genetic tables illustrating an attempt to link the adult form of polycystic renal disease with some other easily recognizable genetic factor. In this investigation it proved impossible to determine a linkage with any particular blood group or factor, nor with the salivary secretion of Haptenes or ability to taste phenylthiocarbamide.

(1957) in a carefully controlled series have indicated that they inevitably lead to some deterioration. Nevertheless, Yates Bell (1957) in this country has provided evidence that the progression of the disease may possibly be retarded in some cases by the performance of Rovsing's operation and there is no doubt that severe pain can often be relieved in this way. It is well to remember, however, that in cases already complicated by serious renal failure, as well as in those associated with hypertension, the risks may not be inconsiderable.

Neo-natal polycystic disease

Having described a number of features which characterize adult polycystic disease it is now possible to consider its relationship to the neo-natal form. For this purpose some of the reasons previously advanced for suggesting that the two conditions are distinct (Fergusson, 1949) are recapitulated. In the first place the marked difference in age incidence is difficult to explain on an equivalent genetic basis. Secondly, there can be little doubt that the group of neo-natal cases represents a pathological hotch-potch into which a variety of atypical cystic conditions is thrown, and this in fact enormously exaggerates its proportional significance. Many of these cases are unilateral and complicated by other developmental defects—a state of affairs which is most uncommon in the adult form of the disease. Thirdly, although usually associated with stillbirth or early demise from renal insufficiency the kidneys in neo-natal cases are seldom enlarged to an extent comparable with those causing renal failure in adults and, indeed, may be quite small and uniform in size. Histologically certain differences have also been outlined in the structure and connections of the cysts in the neo-natal and adult forms (Lambert, 1947). Finally, and perhaps of greatest significance, there is at present no certain evidence to support an hereditary basis for the neo-natal condition. While it is true that several members of a particular generation may occasionally be affected, no records exist either of parental or more widespread familial affection. In two cases of neo-natal cystic disease personally observed, the parents (all over the age of thirty) were carefully investigated both clinically and radiologically without finding any indication of polycystic disease. It seems likely, therefore, that the neo-natal condition, if familial at all, is determined by a recessive gene, or otherwise results from what the geneticists term a " phenocopy "—that is an acquired stimulus occurring during intra-uterine life.

It is for these reasons the hypothesis is advanced that the adult and neo-natal forms of polycystic renal disease are distinct.

SIMPLE CYSTS

In contrast to polycystic disease, simple " solitary " cysts of the kidney are generally single or few in number and seldom involve the parenchyma

to more than a limited extent. Occasionally enclosed within the renal substance they are more often situated superficially and project disproportionately from the cortex thus distorting the renal outline. Having attained a sufficient size, they may then present as round swellings which are often discernible on clinical and radiological examination. As in polycystic disease, their presence is seldom suspected before middle life and their clinical incidence increases with advancing age. Opinion remains divided as to their origin from congenital or acquired causes, but there is no indication of any hereditary tendency.

Simple cysts are in general harmless and, although a bilateral distribution is by no means uncommon, the amount of kidney substance involved is never sufficient to threaten life from renal insufficiency. Symptoms are derived from the size and weight of the cyst (or cysts) which may rotate or displace the kidney and cause a sensation of heaviness or dragging pain on the affected side. Clinically detectable cysts commonly vary in size between a tangerine orange and a grapefruit, but even so often fail to induce any significant symptoms or signs. Exceptional cases are on record where a single cyst has filled almost the entire abdomen without occasioning distress.

Many cysts resemble hydroceles in the sense that they seem to progress to a certain size and then fail to advance further. Their response to aspiration, as will be mentioned later, is often also closely similar.

Complications

Although relatively immune to complications certain changes may occasionally take place in simple cysts causing confusion in diagnosis. Among these may be mentioned haemorrhage, calcification and an association with malignant disease.

Haemorrhage into a cyst may be spontaneous, induced by trauma or arise from the coincidental presence of a neoplasm. In a personal case a man of fifty presented with unprovoked painless haematuria which was found on cystoscopy to be derived from the left upper urinary tract. The left kidney was easily palpable and retrograde pyelography showed a large cavity in the upper pole communicating with the renal pelvis. Nephrectomy was performed on the assumption that the bleeding had come from a neoplasm associated with a cyst, but sections merely showed a large simple cyst which had apparently ruptured spontaneously into the renal pelvis.

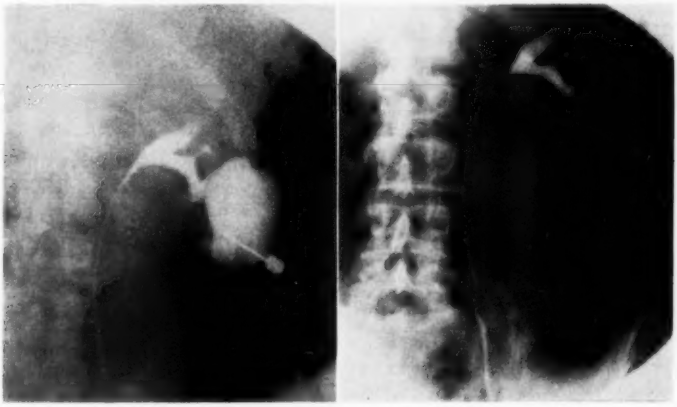
The occurrence of calcification in relation to a rounded renal swelling may also prove extremely misleading. In 1945 a male patient from the Near East underwent an abdominal X-ray examination for symptoms suggestive of mild dyspepsia. The film revealed a crescentic line of

calcification related to the lower pole of the right kidney and a presumptive diagnosis was made of a calcified cyst, possibly of parasitic origin. In the absence of further symptoms and clinical signs he declined exploration and continued well until 1954 when an excretion pyelogram confirmed the previous finding. Exploration was again advised but refused. In May 1958 he experienced slight haematuria and on further examination was found to have a large renal mass. At subsequent nephrectomy the kidney showed a large hypernephroma with extensive curvilinear calcification around the original focus of the tumour (13 years had elapsed since the first radiological evidence of the disease).

Almost identical radiological appearances were shown in another case of a woman of sixty in which a semicircular calcified outline could be seen surrounding a spherical soft-part shadow at the lower pole of the right kidney. Exploration in this instance revealed a simple cyst with numerous deposits of calcium salts on its surface.

Differential diagnosis

Such cases are, however, exceptional and difficulty is more usually experienced in differentiating an *uncomplicated* simple cyst from a more serious lesion. Most swellings of this type are brought to light fortuitously during routine clinical or radiological examination and doubt may often exist as to their harmless nature or otherwise. Clinical examination



(*a*) (*b*)

Fig. 10. Diagnostic aspiration of renal cyst.

(*a*) A needle has been advanced into the cyst cavity which is shown outlined by contrast medium.

(*b*) The same case after aspiration of the contrast material.

is of little help unless the swelling, if palpable, is of sufficient firmness strongly to suggest a tumour. The absence of haematuria or urinary symptoms does little more than favour the presence of a simple cyst and no distinction can be made on the grounds of age or sex. Radiologically a regular circular shadow related to an otherwise normal renal outline gives strong presumptive evidence of a cyst, while the presence of other similar swellings either on the same or opposite side affords additional assurance. Where any element of doubt remains it is customary to advise more detailed investigation either by arteriography, nephrotomography

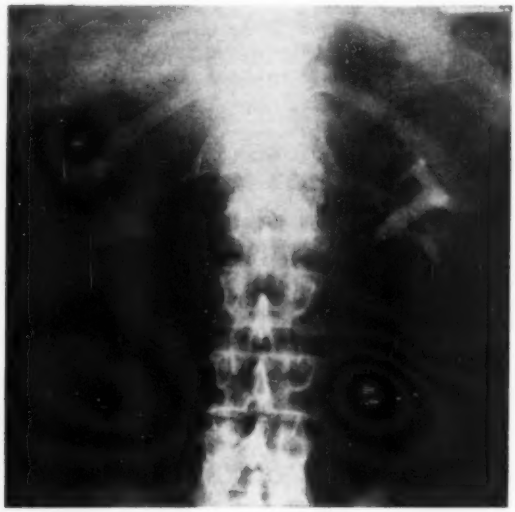


Fig. 11. The same case (see Figs. 10 (*a*) and (*b*)) six months after diagnostic aspiration. Excretion pyelography shows a normal pattern and there is no indication that the cyst has refilled. (In some cases, however, refilling may take place, but this does not necessarily afford an indication for repeated aspiration unless symptoms are present.)

(Southwood and Marshall, 1958) or actual exploration. At this point, careful judgment is often called for to decide whether, in fact, the element of uncertainty is sufficient to justify the possible risk or inconvenience of these procedures. This applies particularly in elderly cases and in those where operation may be contraindicated for other reasons. For selected patients of this kind and others in whom the available evidence strongly suggests a cyst a simple technique of aspiration diagnosis has now been evolved. This consists of preliminary localization of the lesion by pyelography, followed by screening the patient (lying prone) with the X-ray Image Intensifier thus enabling a surface marking to be made immediately

over the presumed cyst. A long aspirating needle, held vertically, is then steadily advanced through the lumbar muscles until it enters the cyst cavity. After partial aspiration a small quantity of contrast medium is injected to demonstrate the smooth outline of the cyst (Fig. 10 (*a*)), thus serving to exclude the remote likelihood of an intra-cavitary neoplasm. Having outlined the cyst in this manner, aspiration is repeated until all fluid has been withdrawn (Fig. 10 (*b*)).

In describing this procedure it must be emphasized that aspiration diagnosis should be undertaken only in carefully selected cases after due regard for the clinical state of the patient and where it is considered improbable that the condition is anything other than a cyst. If aspiration is successful the diagnosis of simple cyst is still not fully confirmed until a further pyelogram shows restoration of a normal pyelogram and normal renal outlines (Fig. 11). If aspiration fails or bloodstained fluid is withdrawn there should be no hesitation in advising exploration as soon as practicable. The simplicity of the procedure, however, is sufficient to commend it as a preliminary or alternative to surgical exploration in suitable cases where the diagnosis is obscure.

ACKNOWLEDGMENTS

I wish to express my indebtedness to Dr. J. J. Stevenson and Dr. F. Pygott of the Departments of Radiology, St. Paul's Hospital and Central Middlesex Hospital, and also to Miss F. M. Wadsworth and Mr. R. E. Bartholomew of the Department of Medical Art at the Institute of Urology for their assistance in preparing the illustrations.

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ADMISSION TO THE HONORARY FELLOWSHIP

The President admitting Dr. Huggins to the Honorary Fellowship, with Mr. A. Dickson Wright, Senior Vice-President, in the background.

AT THE MEETING of the Council on 10th December, Dr. Charles Huggins of Chicago was admitted to the Honorary Fellowship of the College.

Dr. Huggins was presented to the President and Council by Sir Stanford Cade, K.B.E., C.B., Vice-President, who delivered the following citation:

" Mr. President,

" The Council of this Royal College has unanimously recommended that the highest honour it can bestow be awarded to Dr. Charles Huggins. It is now my greatly prized privilege to invite you to admit him to the Honorary Fellowship.

" It may interest you, Mr. President, to learn that, although an American citizen by choice, he is of Scottish ancestry and proud to be the grandson of one Margaret Mackenzie of Glasgow. It is perhaps this Glasgow ancestry, the inherited tenacity of the Scottish race, that sparked off in him the desire to continue the researches of another Glasgow surgeon, George Beatson, who conceived the notion of what he, Charles Huggins, half a century hence, named hormonal dependence of cancer.

" It may also interest you and the Councillors of this College, that he was born in Halifax, Nova Scotia, and is in fact by birth, ancestry and tradition, a citizen of the British Commonwealth of Nations. His formative years were spent in the United States and he graduated from Harvard University in 1924. We all know the place Harvard occupies in medical education and having spent some of your early post-graduate life there your own portrait, Mr. President, now adorns one of the halls of the Peter Bent Brigham Hospital.

" Charles Huggins's natural instinct for research attracted him to London, where at the Institute of Medical Research, Mount Vernon, Hampstead, he spent a considerable time acquiring the knowledge of research methods. This period of his life among us must have influenced him considerably, as a generation later he sent his son, a young surgeon, to spend a year in the research laboratories at Mill Hill.

" On his return to Chicago, Charles Huggins resumed the practice of surgery, and rapidly climbed the academic ladder. In 1936, he was appointed Professor of Surgery of the University of Chicago.

" It has been said of him, that his researches were by design and not by accident. You can trace them throughout the years following a logical pattern, from the physiology of the seminal vesicles, the significance of acid phosphatase, the physiological effects of androgens and oestrogens on the structure and function of the testis to the concept of an indirect attack or the remote control of cancer. These original experiments, carried out with painstaking attention to detail and lucidity of interpretation of cause and effect, an approach through physiology to pathology, were " Hunterian " in their conception and execution. Charles Huggins in fact, after a lapse of a century and a half, picked up the threads of the Hunterian method, and this alone would have made him worthy of the honour you are about to confer on him.

" Fortunately his experiments, step by step, led to the practical applications in cancer therapeutics. We, in this country, are proud that an Englishman, Charles Dodds, has synthetised oestrogens. He, Charles Huggins, has added lustre to American surgery by being the very first to try oestrogens in cancer of the prostate. This trial was not a shot in the dark, it was the cool reasoning of a research mind which logically led to trial; and it was successful. A countless number of men with prostatic cancer have since then been granted an extension of life on earth, which aggregated in years amounts to centuries.

" Many a man, having achieved so much, having opened the portals of a new, indirect, endogenous attack on cancer, would have been content to rest on his laurels, but the Hunterian spirit drove him on. He was the first to conceive the idea of adrenalectomy as a method to ablate the source of steroids. This idea preceded the discovery of Cortisone and his first patients died. He was ahead of his time. The advent of Cortisone permitted him to resume his trials, and now all over the world the surgical hormonal control of cancer of the breast brings relief and hope to many.

" This progress of research by design has continued unabated. As a Director of the Ben May Laboratories, he has dedicated himself selflessly and totally to the problems of cancer of the breast. It is to him we owe the concept of setting carcinogens to attack cancer. His experiments with 3 Methyl Cholanthrene are well known. Even then, not content with this full life of practice, research and experiment, he is devoting himself now to the biological problems of D.N.A. and their significance in the aetiology of neoplastic diseases.

" Few surgeons since Hunter have contributed so much with such brilliance to the relief of suffering mankind. As a man, dedicated to this task of helping humanity, the many honours, degrees, fellowships, medals and awards given to him by a number of Universities, Colleges, Academies and Scientific Societies have left him the quiet, humble, unassuming, self-effacing man who acquires friends by natural instinct.

" Mr. President, I have the honour to ask you to forge a further link across the Atlantic by conferring the Honorary Fellowship of this College on Charles Brenton Huggins, American citizen, Canadian by birth and Scottish by descent; Professor of Surgery of the University of Chicago, Director of the Ben May Laboratories, member of the Order " Pour le Mérite ", Honorary Graduate of the Universities of Leeds, Madrid, Turin, Yale, Washington and of his own original small College, Acadia in Canada. A man whose surgical contributions, Hunterian in their methods, have brought so much relief to the victims of cancer as to make this an equal honour to him who receives it as to us who are conferring it."

IMPERIAL CANCER RESEARCH FUND

LORD SALISBURY HAS agreed to succeed the late Lord Halifax as President of the Fund.

ADMISSION TO THE COURT OF PATRONS

Mr. Williams being admitted to the Court of Patrons by the President, watched by the two Vice-Presidents, Mr. A. Dickson Wright (centre) and Sir Stanford Cade.

AT THE QUARTERLY MEETING of the Council on 14th January, Mr. Leonard J. Williams was admitted to the Court of Patrons. After the Vice-Presidents had presented Mr. Williams to the President and Council, Sir Arthur Porritt spoke as follows:

" Mr. President : As a classical example of an old classical dictum *multum in parvo*, I present to you Mr. Leonard John Williams. Mr. Williams surely needs no introduction to this Council, for during the past three-and-a-half years or more he has given to the Finance Committee and the Appeal Committee of this College most valuable advice and direction. It is, I think, impossible to put into words or, for that matter, into figures the value of the debt we owe him. But I can think of innumerable meetings of the Finance Committee when his advice on matters of finance and of investments have raised not only the admiration, but also the respect and the gratitude of the members of that Committee. His never-failing patience in directing our frequently faltering financial footsteps and his constantly charming company and his natural bonhomie have endeared him to all of us on the Appeal Committee also. His sound counsel and his extremely wide knowledge of the world of business, finance, commerce and industry has been an invaluable asset, and when you add to all that the fact that he himself has been responsible for bringing to our Appeal Fund a figure that approximates as nearly as nothing to £100,000, you will realize that Mr. Williams is very near to the heart of the College.

" It will not, therefore, surprise you, I am sure, to hear that he is a well-known banker. For many years he was the Chief General Manager of the National Provincial Bank and when he retired from that position he became one of the Board's Directors. In February 1956, when the Finance Committee decided that the financial affairs of the College demanded more specialized knowledge, a decision wisely endorsed by the Council, what more excellent example of the financial world could we have had than Mr. L. J. Williams. I may say also that his appearance in the College created history

for, if I am right, he was the first layman to be appointed to a statutory committee of this College. We certainly learned during those three years that he was a man of sterling quality, that his principles were unshakable and that his loyalty was very great. I know that he, with his innate modesty, is blissfully unaware of what I have been saying, and I equally well know that I shall never be forgiven for presuming to the extent that I have, but I must ask his forgiveness and pass quickly over to other aspects.

" He has a pawky sense of humour, mixed with Welsh sentimentality ; he is an experienced bridge player, a connoisseur and a lover of good food, good wine and good company ; and probably not many of you know of his winter activity of a cruise to the summer climes. This I would like to say—and I think he would agree—that in all these activities he has been blessed by a happy home and family life. May I, on your behalf, Mr. President, welcome Mrs. Williams, whom we are delighted to have with us today.

" We have made, and hope we will keep, a very good friend of this College, someone who has devoted himself to the welfare and wellbeing of this College in a manner which amply merits the membership of our Court of Patrons, and to that end I have the honour and the pleasure to present Mr. L. J. Williams."

The President, admitting Mr. Williams to the Court of Patrons, referred to his abiding interest in the affairs of the College and expressed the hope of the members of the Council that Mr. Williams would visit the College frequently.

Mr. Williams then addressed the President and Council:

" Mr. President, Sir Arthur, Members of Council : This is a tremendous occasion in my life, and at the same time something of an ordeal for me, but let me say that in this familiar setting and in the presence of so many friendly faces I can at least feel that I am very much at home in a lot of ways. Your citation, Sir Arthur, is far too generous, exceeding anything that I can deserve or ever will deserve. You ask for my forgiveness : that is given in full measure because, if I may say so here, Mr. President, I can never repay the debt of gratitude I owe to Sir Arthur Porritt.

" I am very conscious and very proud of the very great and totally unexpected honour you have conferred on me this day, and really I don't know that there is much more that I can say about that, but I shall treasure the memory of this day and I thank you, Sir, and the members of the Council, most sincerely and most humbly for this honour that you have conferred upon me today. Let me say in conclusion quite briefly that I hope and think that I have not yet exhausted my efforts on behalf of the College. Thank you very much indeed."

ANNUAL MEETING OF FELLOWS AND MEMBERS

THE ANNUAL MEETING of the College was held on Wednesday, 9th December, at the College. The Scientific Departments were on view throughout the day and visitors were able to see the research work being carried on at the College. They were also able to attend two lectures in the Course in the Basic Medical Sciences, one on " The anatomy of the foot ", by Dr. F. Stansfield, and the other on " The physiology of pain and its surgical treatment ", by Dr. B. D. Wyke, and a series of scientific films which were shown in the Cuthbert Wallace Room.

The first Watson-Jones Lecture was delivered in the afternoon by the Rt. Hon. Lord Cohen of Birkenhead, who chose as his title " Reflections

on specialism in medicine". It is hoped to publish this lecture in a forthcoming issue of the *Annals*.

The Annual Meeting of Fellows and Members took place at 3.30 p.m., when the Agenda was as follows :—

1. The President to report on the affairs of the College during the period from 1st July 1958 to 31st July 1959.
2. Report on the financial position of the College.
   Opener : Sir Arthur Porritt, K.C.M.G., K.C.V.O., C.B.E., F.R.C.S., Chairman of the Finance Committee.
3. Report on the progress of the rebuilding of the College.
   Opener : Sir Eric Riches, M.S., F.R.C.S., Chairman of the Building Committee.
4. Report on the Appeal of the College.
   Opener : Sir Archibald McIndoe, C.B.E., F.R.C.S.
5. A showing of the film " Healing Hands".

After the meeting was over, tea was served, and this was followed by a talk on the history of the College and its Charters, given by Sir Zachary Cope, F.R.C.S.

The Monthly Dinner of the College was held in the Edward Lumley Hall at 7.30 p.m., and was very well attended. This was followed by a second showing of the film " Healing Hands " and afterwards the guests were able to visit the Scientific Departments and the Library, which were still on view.

Readers may be interested to see the following letter which was received by the President, Professor Sir James Paterson Ross, Bt., K.C.V.O. The writer is a Fellow who obtained his Fellowship in 1956.

" Dear Sir James,

" A short note to say how much I enjoyed the first Annual Meeting I have been able to attend and I am now sorry I have missed them before. Perhaps it should be called View Day or Old Boys' Day.

" It was very interesting to see and hear at first hand of the many aspects of the work of the College and the results obtained by the efforts of so many people. I feel it is to their loss that more of the younger Fellows were unable to attend. In addition to the first-class lectures they would have also learnt more about the use to which their money is being put and the use we can make of the College facilities—including guidance and help. I for one did not fully realize, and I am sure I am not alone, all that goes on or can be had at 39-43 Lincoln's Inn Fields. I am afraid we envisage it as an examination torture chamber and forget to enjoy its friendship.

" I hope Lord Cohen's oration will be published.

" Many thanks for an enjoyable View Day.

" Yours sincerely,

" N.G.R."

ANATOMICAL MUSEUM

THE SPECIAL DISPLAY for the month of February consists of a selection of the microscopical preparation of John Thomas Quekett, Conservator of the Hunterian Museum from 1856 to 1861.

BOOKS ADDED TO THE LIBRARY

July—December 1959

BASIC SCIENCES

Anatomy

JAMIESON. Illustrations of anatomy. 8th edition.
LAST. Anatomy, regional and applied. 2nd edition.
VAN DER EECKEN. Anastomoses between leptomeningeal arteries.
JACOBS. Arterial embolism in the limbs: anatomical basis.
HUTCH. The ureterovesical junction.
BARSKY. Congenital anomalies of the hand.
BYRNE. The hand: anatomy and diseases.
GREULICH AND PYLE. Skeletal development of hand and wrist. 2nd edition.
ESTRADE. Anomalies of intestinal rotation.

Anatomy, comparative

ROMER. The vertebrate story.

Bacteriology

FAIRBROTHER. Textbook of bacteriology. 8th edition.
GRAINGER. A guide to the history of bacteriology.
BURNET. The Viruses. 3 vols.

Biochemistry

MUHLER. Textbook of biochemistry for students of dentistry.
PAGE (editor). Chemistry of lipides as related to atherosclerosis.
PITT-RIVERS AND TATA. The thyroid hormones.

Biological Research

ATKINS (editor). Tools of biological research. Gift of Mr. H. J. B. Atkins.
RUSSELL AND BURCH. Principles of humane experimental research.
BAILEY. Statistical methods in biology.
FISHER. Statistical methods and scientific inference. 2nd edition.

Cancer Research

BLUEFARB. Cutaneous manifestations of malignant lymphomas.
DELARIO. Breast cancer: factors modifying prognosis.
HOMBURGER. Physiopathology of cancer. 2nd edition.
MAKAR. Pathogenesis of cancer of the Bilharzial bladder 1950. Gift of Sir Cecil Wakeley.
MALCOLM. Aetiology of melanotic cancer.
WYBURN-MASON. Reticulo-endothelial system in growth and tumour formation.

Cytology

CIBA Symposium on Regulation of cell metabolism.
MELLORS. Analytical cytology. 2nd edition.
PALAY. Frontiers in cytology.
PRICE (editor). Dynamics of proliferating tissues.
SWANSON. Cytology and cytogenetics.

Development

BEATTY. Parthenogenesis and polyploidy in mammalian development.
MCELROY AND GLASS (editors). Chemical basis of development.
Developmental Biology Conference series:
DUCOFF. Mitogenesis.
EDDS. Immunology and development.
RUDNICK. Cyto-differentiation.
THORNTON. Regeneration in vertebrates.

Endocrinology

LLOYD. Recent advances in endocrinology of reproduction.

Genetics

PENROSE. Outline of human genetics.

Pathology

LANDELLS. Essential principles of pathology.
CROHN AND YARNIS. Regional ileitis. 2nd edition.
ILLINGWORTH. Recent advances in cerebral palsy.
MEYER. Oesteo-radio-necrosis of the jaws.
ATLAS AND GABERMAN. Reversible renal insufficiency.
MUNCK. Renal circulation in acute renal failure.
OSSERMAN. Myasthenia gravis.
TERRACOL. Diseases of the oesophagus.

Pharmacology

CLARK'S Applied Pharmacology. 9th edition.

Physiology

BAYLISS. Principles of general physiology. New edition. Vol. 1.
BEST AND TAYLOR. The living body. 4th edition.
DAVSON. A textbook of general physiology. 2nd edition.
JAMIESON AND KAY. Textbook of surgical physiology.
PATTERSON. Wound healing and tissue repair.
BROOKS AND CRANEFIELD (editors). The historical development of physiological thought.

CLINICAL SUBJECTS

Anaesthesia

HARBORD AND WOOLMER (editors). Pulmonary ventilation.
MUSHIN AND OTHERS. Automatic ventilation of the lungs.
WYLIE AND CHURCHILL-DAVIDSON. A practice of anaesthesia. (The last two presented by Professor R. Woolmer.)

Dental Research

MOORREES. The dentition of the growing child.
SMITH. A short history of dentistry.

Dermatology

MACKEY. Handbook of diseases of the skin. 6th edition. Author's gift.
BEAN. Vascular spiders and related lesions of the skin.

Neurology

BRODAL. Cranial nerves: anatomy, etc.
CARTON. Cerebral angiography in head trauma.
COERS AND WOLF. Innervation of muscle.
CONEL. Post-natal development of the human cerebral cortex, vol. 6. Continuation of series.
JASPER (editor). Reticular formation of brain.
LASSEK. The human brain from primitive to modern.
MONRO. Sympathectomy: an anatomical and physiological study.
PENFIELD AND ROBERTS. Speech and brain mechanisms.
RUSSELL. Brain, memory, learning.
RIESE. A history of neurology.

Ophthalmology

RODGER. Blindness in West Africa. Gift of the Royal Commonwealth Society for the Blind.

Orthopaedics

AEGERTER AND KIRKPATRICK. Orthopaedic diseases.
FLATT. The care of minor hand injuries.
ROAF AND OTHERS. Surgical treatment of bone and joint tuberculosis.
STEINDLER. The interpretation of pain in orthopedic practice. Posthumous publication, presented by Mrs. Arthur Steindler.

Otolaryngology

DAMSTÉ. Oesophageal speech after laryngectomy.
DEGELS. Technique of surgical treatment of ozaena. Author's gift.
GRIFFIN. Listening in the dark: acoustic orientation.
HALL. Diseases of nose, throat and ear. 7th edition.
SHAMBAUGH. Surgery of the ear.

Radiology

SHANKS AND KERLEY. Textbook of X-ray diagnosis. 3rd edition, vol. 4 (continuation).

Surgery

JOHNSON (editor). Surgical aspects of medicine.
SOUTTAR AND GOLIGHER (editors). Textbook of British Surgery, vol. 4 (completion of series). Gift of Messrs. Heinemann.
TAYLOR (editor). Recent advances in surgery. 5th edition.
U.S. ARMY MEDICAL DEPT. General surgery in World War II. 1955. Gift of Sir Zachary Cope.
ADDIANI AND PARMLEY. The recovery room.
JENTSCHURA (editor). Beschäftingungstherapie. Gift of Sir Henry Souttar, who has also given fifty older textbooks of surgery, etc.
BACON. Ulcerative colitis.
THACKER. Postural drainage. 2nd edition.
PEER. Transplantation of tissues, vol. 2. (Vol. I published and bought in 1955.)
D'ABREU. A practice of thoracic surgery. 2nd edition.
BADEN. Surgical treatment of mitral stenosis.
EAST AND BAIN. Recent advances in cardiology. 5th edition.
STEWART AND GLENN. Mitral valvulotomy.
DOHERTY. Surgical equipment [Catalogue]. Publisher's gift.
LONDON SPLINT CO. Catalogue. Publisher's gift.

HISTORICAL COLLECTION

Historic texts

Sixteenth century

BERENGARIO DA CARPI. A short introduction to anatomy, translated and edited by Lind and Roofe.
O'MALLEY. The Anatomy of Thomas Geminus, with a facsimile.
THE ORDER OF THE HOSPITALS 1557 (1691?). Gift of Mr. Philip Wiles.
PARÉ. Oeuvres. 1575. Gift of Mr. E. G. Greville, M.C., M.R.C.S. The first collected edition in a contemporary binding.
VESALIUS' first public anatomy, reported by B. Heseler 1540, edited and translated by R. Eriksson.

Seventeenth century

GUILLEMEAU. Oeuvres. 1612. Gift of Mr. E. G. Greville, with the Paré listed above.
WISEMAN. Severall chirurgicall treatises. 1676. First edition, presented by MRS. P. G. Doyne.

Eighteenth century

BAKER. The microscope made easy. 2nd edition. 1743.
GALVANI. On electricity in muscular movement, 1791, edited with a facsimile, 1953. Gift of Mr. Bern Dibner, Burndy Library, Connecticut.
WALTER. Plates of the thoracic and abdominal nerves (1783), translated 1822. Gift of Sir Russell Brock.

Nineteenth century

ABERNETHY. Surgical observations on diseases resembling syphilis. 1810.
COCKS. Operative surgery. 1837.
MACNALTY. The Sue family of surgeons. A collection of books and articles, gift of Sir Arthur MacNalty.
MILES. Health promoted with regard to the teeth. 1846. Gift of Dr. J. Menzies Campbell, Hon. F.F.A.R.C.S., for the L.D.S. Centenary.
New Sydenham Society's Biennial Retrospect 1873-74, containing articles by Lord Lister. Gift of Mr. C. D'Oyly Grange, F.R.C.S.
TOMES. Lectures on dental physiology and surgery. 1848. Gift of Sir Wilfred Fish.

History, etc., of Science and Medicine

BATESON. The convict ships 1788-1868, with complete lists of ships' surgeons.
COPPLESON. Shark attack. Author's gift.
FEILING. History of the Maida Vale Hospital.
SARTON. History of Science: vol. 2 — Hellenistic science.
SINGER. Short history of scientific ideas.
STEVENSON. The meaning of poison. Clendening lectures, University of Kansas. Publisher's gift.
VAUGHAN. Doctor's Commons. History of the B.M.A.

Biography

BAILEY AND BISHOP. Notable names in medicine and surgery. 3rd edition.
CHIENE. Looking back 1907-1860 [Memories of Edinburgh medical school]. Gift of Sir Zachary Cope.
NEJDL. Jean de Carro. Gift of Professor V. Kruta of Brno.
HIMMELFARB. Darwin and the Darwinian revolution.
MCMENEMEY. Life and times of Sir Charles Hastings.
FISK. Dr. Jenner of Berkeley.
PAGEL. Paracelsus.
WHITESIDE. The nomadic life of a surgeon. 1950. Gift of the author, W. Carleton Whiteside, F.R.C.S.(C.).

HOWARD GRAY MEMORIAL LIBRARY

Third list of gifts presented through Mr. A. Dickson Wright

Holy Bible. Brown's self-interpreting edition. New York (1859). Presented, in a special binding, by Mrs. Howard Gray.
Cruden's Concordance of the Old and New Testaments.
Burke's Peerage. 102nd edition.
International Who's Who 1959.
The Middle East. 1959.
Larousse Encyclopaedia of Mythology.
Grimal. Dictionnaire des Biographies. 2 vols.
Edmunds. Ideals in medicine. Gift of Dr. W. R. Burkitt.
Evelyn's Diary, edited by E. S. de Beer. (Single volume edition.)
Hickey's Memoirs 1749-1809. (1913-25.) 4 vols.
Russell. Wisdom of the West.

THE HUNTERIAN TRUSTEES

WE REGRET AN error in the short article about the Hunterian Trustees, published in the November 1959 issue of the *Annals*. The date of Sir Hugh Lett's election to the office of Chairman of the Hunterian Trustees should have been given as 1955 and not 1956. The length of Sir Hugh's term of office was four years.

RECENT OVERSEAS VISITORS TO THE COLLEGE

RECENT OVERSEAS VISITORS to the College have included Dr. E. G. Sayers, C.M.G., Past President of the Royal Australasian College of Physicians, who stayed in the Visiting Professors' Flat in the Nuffield College, and Professor John Loewenthal, F.R.C.S., Professor of Surgery in the University of Sydney.

HONOURS CONFERRED ON FELLOWS AND MEMBERS

In the recent New Year Honours List the following Fellows and Members were graciously honoured by Her Majesty The Queen.

Sir James Paterson Ross, K.C.V.O., M.S., President of the College	Baronet
Ivan Whiteside Magill, C.V.O., F.R.C.S., Hon. F.F.A.R.C.S.	K.C.M.G.
John Patrick Walsh, F.D.S.R.C.S.	K.B.E.
Professor Andrew M. Claye, M.D., F.R.C.S., President of the Royal College of Obstetricians and Gynaecologists	Knight Bachelor
Air Commodore W. P. Stamm, F.R.C.P., M.R.C.S., Q.H.S.	C.B.E. (Milit.)
Louis Abel Célestin, M.C., M.D., M.R.C.S.	C.B.E. (Civil)
Professor Robert Wilfred Scarff, F.R.S.Ed., F.R.C.S.	,, ,,
Leonard Anthony Paul Slinger, O.B.E., M.R.C.S.	,, ,,
Stanley Walker Cooper, F.R.C.S.Ed., M.R.C.S.	O.B.E. (Civil)
Elizabeth Theodora Mess, F.R.C.S. Ed., M.R.C.S.	,, ,,
Eileen Rosamund Barter Snow, M.R.C.S.	,, ,,
Douglas Eric Thompson, M.R.C.S.	,, ,,
Basil Dudley Whitworth, M.R.C.S.	,, ,,
Walter Parker Harrison, M.R.C.S.	M.B.E. (Civil)
William Alfred Conrad Hortor, M.R.C.S.	,, ,,

APPOINTMENT OF FELLOWS AND MEMBERS TO CONSULTANT POSTS

V. G. MAVALANKAR, F.R.C.S.	Honorary Assistant Surgeon to Civil Hospital and B.J. Medical College, Ahmedabad.
JEAN M. HORTON, F.F.A.R.C.S.	Consultant Anaesthetist to Western General Hospital, Edinburgh, and Edinburgh Royal Infirmary.
J. W. JACKSON, F.R.C.S.	Thoracic Surgeon to Harefield Hospital.
H. F. SMITH, F.R.C.S.	Consultant Surgeon to Blackpool and Fylde Group of Hospitals.
J. A. HANLEY, F.R.C.S.	Surgeon to Sheil Hospital, County Donegal.

The Editor is always glad to receive details of new appointments obtained by Fellows and Members, either through the Hospital Boards or direct.

PROCEEDINGS OF THE COUNCIL IN JANUARY

AT A MEETING of the Council on 14th January 1960, with Professor Sir James Paterson Ross, Bt., President, in the Chair, Mr. L. J. Williams was admitted to the Court of Patrons. Mr. Williams, who was formerly Chief General Manager of the National Provincial Bank, has given the College noteworthy service as a member of the Finance and Appeal Committees, and has been instrumental in attracting to the College gifts to the value of nearly £100,000.

The Honorary Fellowship of the College was awarded to Professor Carl Semb, of Oslo.

The following were elected Members of the Court of Patrons :

Sir Cecil Wakeley, Bt., Past President
Sir Harry Platt, Bt., Past President
Mr. W. Arnold Innes, benefactor of the College
Mr. Cecil R. Coleman, benefactor, and founder of the Lilian May Coleman Fund for Cancer Research.

Professor A. W. Wilkinson, Nuffield Professor of Paediatric Surgery at the Institute of Child Health, and Surgeon to the Great Ormond Street Hospital, was formally admitted to the Fellowship, having previously been elected by the Council to that status *ad eundem*.

Mr. H. J. Seddon was appointed Robert Jones Lecturer for 1960, and the President reported that he had awarded a Moynihan Lectureship to Professor Fernand Orban, of Liège, who will lecture on " New Trends in the Treatment of Thrombo-Angeiosis " (Buerger's disease) on Wednesday, 9th March. It was also agreed that a College Lecture should be delivered in July by Mr. Douglas Robb, of New Zealand, who will then be in this country on his tour as Commonwealth Travelling Professor.

Arising from the report of the Board of the Faculty of Anaesthetists, the Honorary Fellowship in that Faculty was awarded to Mr. A. D. Marston, formerly Director of the Department of Anaesthetists at Guy's Hospital and the first Dean of the Faculty, and to Sir Henry Dale, Chairman of the Wellcome Trust and formerly President of the Royal Society. The appointment of Dr. R. P. W. Shackleton as Frederic Hewitt Lecturer for 1961 was confirmed.

Arising from the report of the Library Committee, a vote of thanks was passed to Mr. W. R. Le Fanu, the Librarian, for the enormous amount of research and work which he has devoted to the publication of the new catalogue of portraits. Mr. A. M. Shadrake was appointed Chief Library Assistant.

A Licence in Dental Surgery was granted to one candidate.

The following Diplomas were granted, jointly with the Royal College of Physicians : *Laryngology and Otology* (18) ; *Anaesthetics* (76) ; *Medical Radio-Diagnosis* (37) ; *Medical Radiotherapy* (13) ; *Psychological Medicine* (63) ; *Pathology* (5) ; *Public Health* (18) ; *Tropical Medicine and Hygiene* (9) ; *Child Health* (1).

The following hospitals were recognized under paragraph 23 of the Fellowship Regulations :

Hospitals	Posts Recognized		
	General (6 mths. unless otherwise stated)	Casualty (all 6 mths.)	Unspecified (all 6 mths.)
Tynemouth—Victoria Jubilee Infirmary (additional)			House Surgeon (Orthopaedic)
Hartlepools Hospital (additional)		H.O. (Orth. and Cas.)	
Blackpool—Victoria Hospital (redesignation)			*Under para.* 23 (*b*) *Redesignation of* S.H.O. *as* J.H.M.O.
Epping—St. Margaret's Hospital (redesignation)	*Redesignation of* S.H.O. *as* Regr.		

DIARY FOR FEBRUARY

Thur. 11		D.Phys.Med. Examination (Part I) begins.
	9.30	Dr. A. H. Galley—The newer anaesthetic agents.
	11.00	Dr. G. Jackson Rees—Anaesthesia for children—I.
	2.00	Dr. G. Jackson Rees—Anaesthesia for children—II.
	2.00	Ordinary Council.
	3.30	Dr. R. I. W. Ballantine—Anaesthesia for neurosurgery.
	5.00	Dr. Bradley L. Coley—Moynihan Lecture—Tumours of cartilaginous origin.*
Fri. 12	9.30	Dr. J. F. Nunn—Anaesthesia for patients with chronic respiratory disease.
	11.00	Prof. T. C. Gray—Mechanisms of neuromuscular block.
	2.00	Prof. T. C. Gray—Muscle relaxants in anaesthetic practice—I.
	3.30	Prof. T. C. Gray—Muscle relaxants in anaesthetic practice—II.
Mon. 15	9.30	Dr. J. R. Vane—The principles involved in the use of antidotes in anaesthesia.
	11.00	Dr. W. S. McConnell—General anaesthetic techniques in dental surgery.
	2.00	Mr. L. P. Le Quesne—Fluid balance—I.
	3.30	Mr. L. P. Le Quesne—Fluid balance—II.
		Course in clinical surgery begins.
Tues. 16	9.30	Dr. H. C. Churchill-Davidson—Principles of hibernation and hypothermia—I.
	11.00	Dr. H. C. Churchill-Davidson—Principles of hibernation and hypothermia—II.
	2.00	Dr. R. Bryce-Smith—Anaesthesia and analgesia in obstetrics.

DIARY FOR FEBRUARY

	3.30	Dr. R. Bryce-Smith—An appraisement of local analgesic procedures.
	5.00	Professor A. Sorsby—Ophthalmology Lecture—The optical components during the growth of the eye.*
Wed. 17		D.M.R.D. Examination (Part I) and D.M.R.T. Examination (Part I) begin.
	9.30	Dr. A. I. Parry Brown—Anaesthesia for thoracic surgery.
	11.00	Dr. A. I. Parry Brown—Anaesthesia for cardiac surgery.
Thur. 18		D. Phys. Med. Examination (Part II) begins.
	9.30	Dr. J. W. Thompson—Local anaesthetics.
	11.00	Prof. A. Kekwick—The assessment of cardiovascular disease.
	2.00	Dr. H. G. Epstein—Aspects of physics in relation to anaesthetics—I.
	3.30	Dr. H. G. Epstein—Aspects of physics in relation to anaesthetics—II.
	5.00	Dr. M. O. Skelton—Erasmus Wilson Demonstration—Some pathological conditions of the pulmonary tissues.*
Fri. 19	9.30	Prof. E. A. Pask—Oxygen therapy.
	11.00	Prof. E. A. Pask—Mechanisms of anaesthesia.
	2.00	Dr. A. Crampton Smith—Tetanus.
	3.30	Dr. Russell M. Davies—Anaesthesia for plastic surgery. Course in Anaesthetics ends.
Wed. 24		Primary F.D.S. Examination, D.M.R.D. Examination (Part II), and D.M.R.T. Examination begin.

DIARY FOR MARCH

Wed. 2		D. Orth. Examination and D.M.R.T. Examination (Part II) begin.
Thur. 3	5.30	Dr. R. M. B. McKenna—Otolaryngology Lecture.*
Wed. 9		First L.D.S. Examination and D.C.H. Examination begin.
Thur. 10		First Membership Examination begins.
	2.00	Ordinary Council.
	5.00	Professor S. O. Aylett—Hunterian Lecture—Diffuse ulcerative colitis and its treatment by ileorectal anastomosis.*
Wed. 16		Board of Faculty of Anaesthetists.
	3.00	Annual General Meeting of Faculty of Anaesthetists.
	4.00	Dr. J. A. Lee—Joseph Clover Lecture.*
Thur. 17		Pre-Medical Examination begins.
	5.00	Professor Arthur E. Jones—Hunterian Lecture—Supervoltage X-ray therapy of intracranial tumours.*
Fri. 18	5.00	Board of Faculty of Dental Surgery
Tues. 22		Date of election of Fellows to the Board of Faculty of Dental Surgery announced.
	5.00	Mr. J. H. Peacock—Arris and Gale Lecture—Endocrine and metabolic aspects of peripheral blood flow and vasoplastic disease.*
Wed. 23	5.00	Professor Howard H. Eddey—Hunterian Lecture—Cancer of the mouth.*
Thur. 24	5.00	Dr. A. G. Stansfeld—Erasmus Wilson Demonstration.*
Sat. 26		Last day for applications for Annual Examinerships.
Mon. 28	5.00	Dr. R. A. Weale—Edridge-Green Lecture.*
Tues. 29		Final Membership Examination begins. Date of Council Election announced.
Thur. 31	5.30	Mr. D. W. C. Northfield—Otolaryngology Lecture.*

*Not part of courses.

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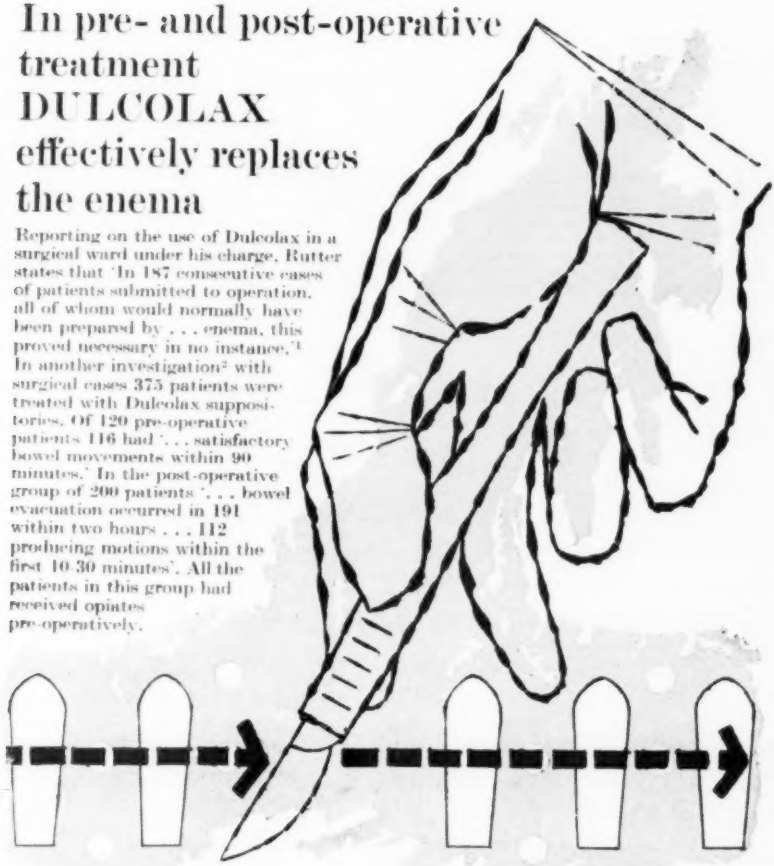

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[1]Rutter, A. G., *Lancet*, 1959, **i**, 1173.
[2]Ganz, P., and Zindler, S., *Medizinische*, 1955, **29-30**, 1042.

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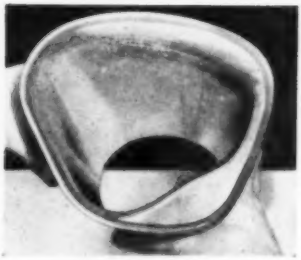

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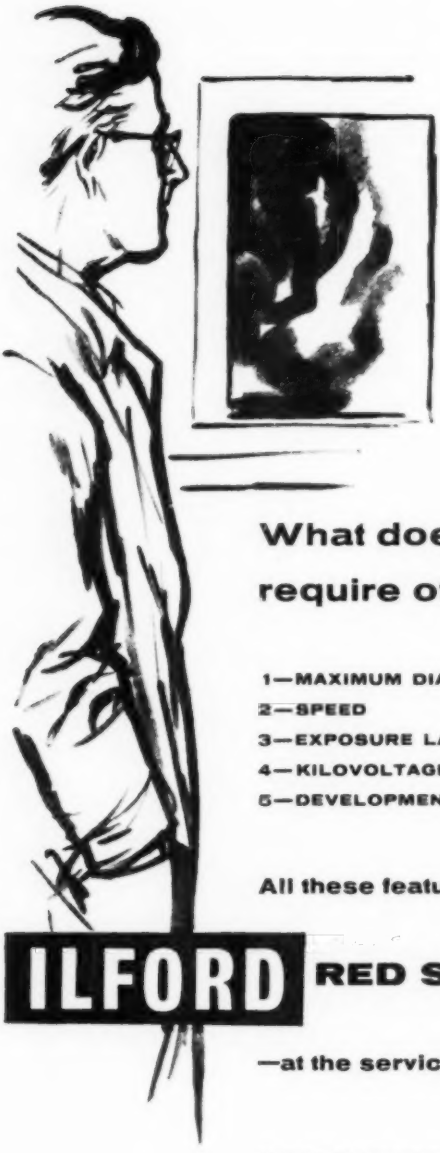

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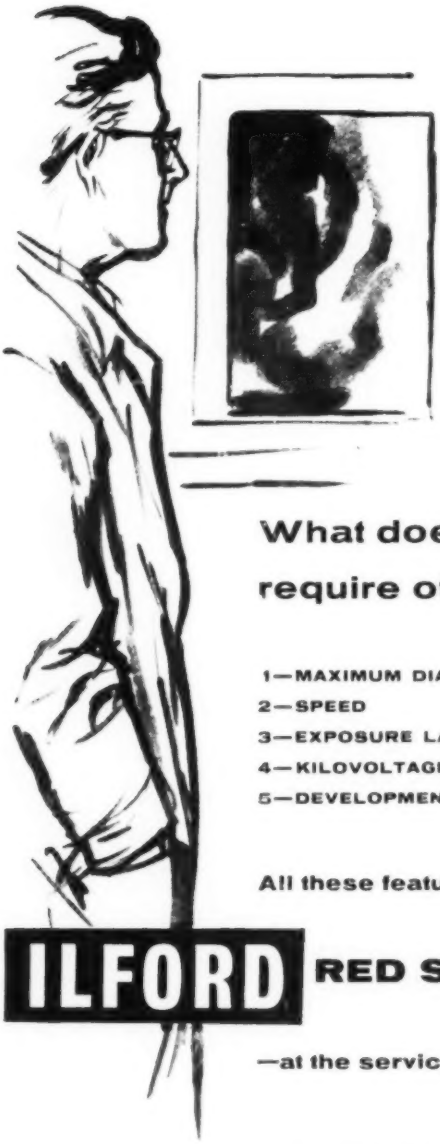

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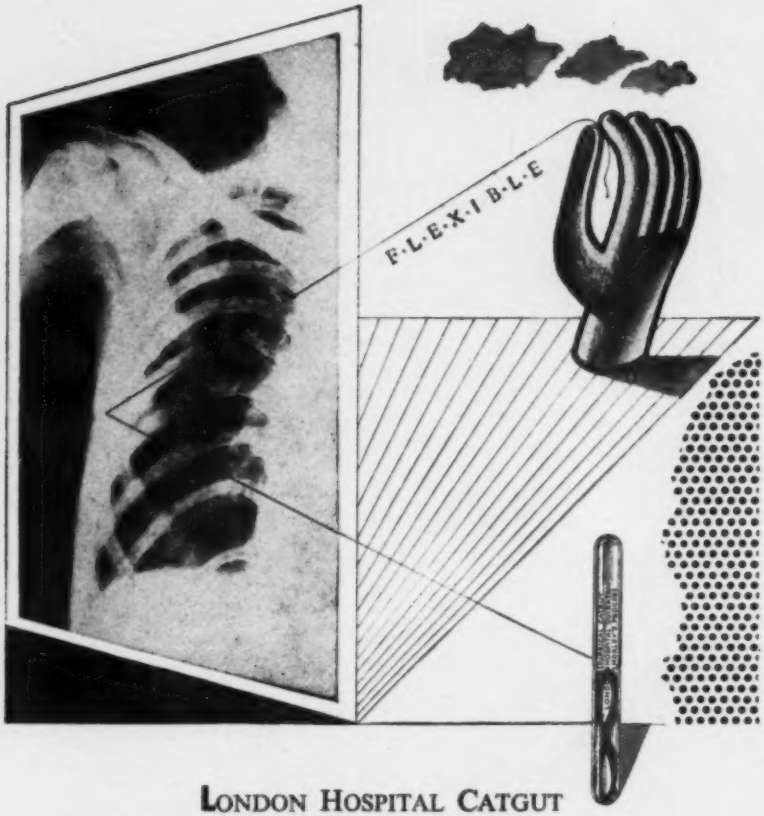

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